

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 May 2002 (10.05.2002)

PCT

(10) International Publication Number
WO 02/36113 A1

(51) International Patent Classification⁷: A61K 31/395,
31/4045, A61P 11/06, 11/08

(21) International Application Number: PCT/SE01/02372

(22) International Filing Date: 30 October 2001 (30.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0003995-8 1 November 2000 (01.11.2000) SE
60/244,661 1 November 2000 (01.11.2000) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CH, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/36113 A1

(54) Title: COMPOSITION COMPRISING: SEROTONIN RECEPTOR ANTAGONISTS (5HT-2, 5HT-3) AND AGONIST (5HT-4)

(57) Abstract: A composition comprising a combination of a) at least one compound with agonist activity to the 5-HT₄ receptor, b) at least one compound with antagonist activity to the 5-HT₃ receptor, and c) at least one compound with antagonist activity to the 5-HT₂ receptor is described.

COMPOSITION COMPRISING: SEROTONIN RECEPTOR ANTAGONISTS (5HT-2, 5HT-3) and agonist (5HT-4)

Field of the Invention

The present invention relates to a composition comprising a combination of a) at least one compound with agonist activity to the 5-HT₄ receptor, b) at least one compound with antagonist activity to the 5-HT₃ receptor and c) at least one compound with antagonist activity to the 5-HT₂ receptor, to a composition as defined above, for use as a medicament, to the use of said composition in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction in humans or animals, and to a method of treatment of such disorders, wherein said compound is administered.

The present application claims priority from the provisional U.S. application No. 60/244,661 and the Swedish patent application No. 0003995-8.

Background of the Invention

There are seven main types of 5-HT (serotonin; 3-(β -aminoethyl)-5-hydroxyindole) receptors, (5-HT₁₋₇). These receptors occur throughout the body, e.g. in the airways, and have mainly been reported to be of significance in conjunction with treatment of CNS, muscle and gastric disorders. In such treatments, compounds with agonist activity to a 5-HT₁ type receptor are often used. For a recent review of 5-HT receptors, see Gerhardt, C.C. & van Heerikhuizen, H., Eur. J. Pharm., 334, 1-23 (1997), which is incorporated herein by reference. For a review of typical agonists and antagonists of various 5-HT receptors, see R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference. Further information regarding 5-HT receptors and their agonists and antagonists can be found in the RBI Handbook of Receptor Classification and Signal Transduction, 3rd Edition, 1998, RBI, One Strath-

more Road, Natick, MA 01760-2447, USA, Editor: Keith J. Watling, which is also incorporated herein by reference.

SU 1 701 320 A1 proposes the use of the unspecific 5-HT for treatment of acute asthma attacks. However, from 5 our and other groups' results (see below), it appears obvious that 5-HT is unsuitable for use alone as a treatment for said disease.

Disclosure of the Invention

The present invention is based on the novel finding 10 that certain 5-HT receptors are of the utmost importance in determining the level of airway constriction. In summary, it is disclosed herein that the administration of a composition comprising a combination of a) at least one compound with agonist activity to the 5-HT₁ receptor, b) 15 at least one compound with antagonist activity to the 5-HT₃ receptor and c) at least one compound with antagonist activity to the 5-HT₂ receptor, causes an almost complete airway relaxation, and is therefore suitable as an agent for treatment of disorders involving airway constriction. A method for treatment of disorders involving 20 airway constriction is also disclosed.

As used herein, the expression "airway constriction" refers to an abnormal increase of force development of 25 the smooth muscle in human or animal airways, resulting in a reduced diameter in some or all of the airways, such as occurring in asthma, chronic obstructive pulmonary disease, emphysema and chronic bronchitis. Said expression also refers, in a wider sense, to a reduction of 30 airway diameter caused by swelling, oedema, plasma extravasation or mucous secretion caused by e.g. asthma or any other disorder related thereto.

The expression "has the capacity of reducing the abnormal airway constriction by at least%" used in the present patent application means that the combination of 35 compounds in question reduces, in a certain degree, airway constriction caused either by (1) the underlying disease (asthma etc) or (2) the administration of 5-HT or

other substances capable of activating constricting 5-HT receptors. The level of constriction in the airways can e.g. be determined by spirometric measurements of the Forced Expiratory Volume in 1 second (FEV1), compared to 5 the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV1 during periods of relatively little obstructive problems.

10 The present invention relates, in one of its aspects, to a composition comprising a combination of compounds comprising a) one or several compounds with agonist activity to the 5-HT₄ receptor, b) one or several compounds with antagonist activity to the 5-HT₃ receptor, and c) one or several compounds with antagonist activity 15 to the 5-HT₂ receptor.

In another aspect, the present invention relates to a composition as defined above for use as a medicament.

20 In still another aspect it relates to the use of said composition in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving airway constriction, such as asthma, chronic obstructive pulmonary disease, emphysema and chronic bronchitis.

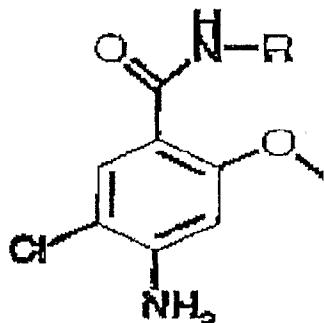
25 In a preferred embodiment said compound with agonist activity is 5-HT or a derivative thereof with agonist activity to the 5-HT₄ receptor. The combination of a) one or several 5-HT₄ receptor agonist(s), b) one or several 5-HT₃ receptor antagonist(s), and c) one or several 5-HT₂ receptor antagonist(s) increases airway relaxation compared to the use of either compound alone, wherein said 30 combination has the capacity of reducing the abnormal airway constriction by at least 30%, preferably at least 60%, and most preferably at least 90%.

35 According to the present invention several known substances are able to stimulate the relaxing 5-HT₄ receptor, without significantly activating the constricting

5-HT₃ and 5-HT₂ receptors, thereby causing airway relaxation. Such agonist compounds are selected from the groups defined below.

Most of the different 5-HT₄ agonists can be referred 5 to specific groups, where each group contains a common structural element. The largest group, and also the basis for several others, are the benzamides. They all contain the structural element 4-amino-5-chloro-2-methoxy benz- 10 amide and are further developments of the first 5-HT₄ agonist, metoclopramide, with the structural formula:

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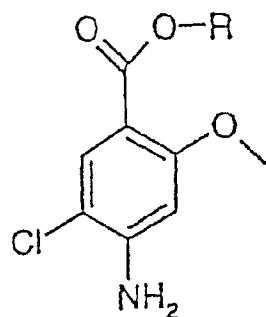
20 Another common feature is a basic nitrogen in a side chain from the amide nitrogen. This basic nitrogen is often a part of a sterically locked system. Examples of substances from this group are: BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, 25 R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, Zacropride.

30 Thus, a structure-activity relation study performed indicates that a benzene ring and a basic nitrogen in the same plane as the ring and at a distance of 8±1 Å from the center of the benzene ring is required. The nitrogen should be locked in that position with a view to obtaining selectivity for the 5-HT₄ receptor. A lipophilic group on the basic nitrogen also seems to be important 35 for the agonistic action. Further, a heteroatom with a free electron pair close to the indole nitrogen in tryptamine seems to give a positive effect.

Benzoic acid esters are modifications of the benzamide theme:

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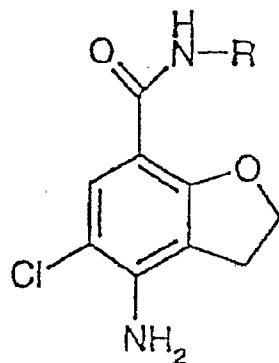
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The only difference is that the amide group has been replaced with an ester group. Examples are ML 10302, RS 15 57639, and SR 59768.

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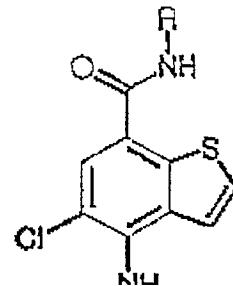
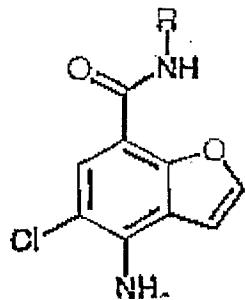
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Benzofuranes and benzotriophenes are also contemplated,

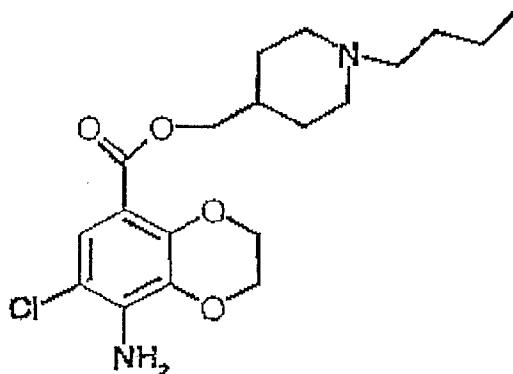
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as well as the benzodioxan

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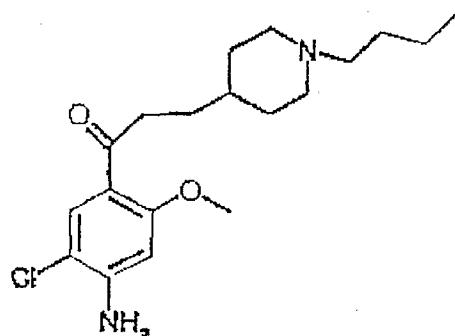
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SB 204070

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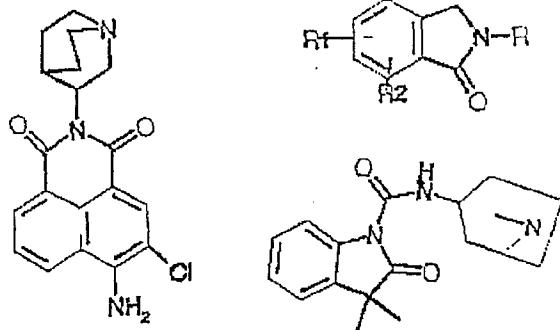


25 e.g. RS 67333 and RS 17017.

The basic concept also applies for naphtalimides,
e.g. RS 56532.

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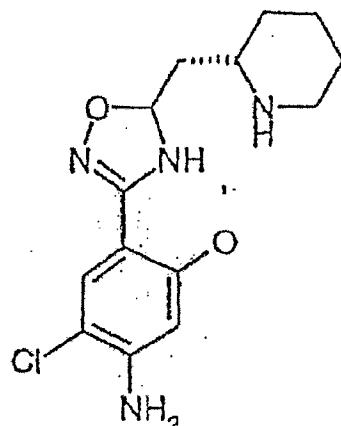


Benzindolones are also contemplated.

The amide function may also be replaced with an oxadiazol ring.

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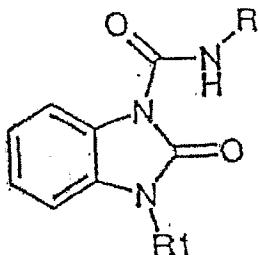
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15 e.g. YM-53389

Benzimidazolone-1-carboxamides

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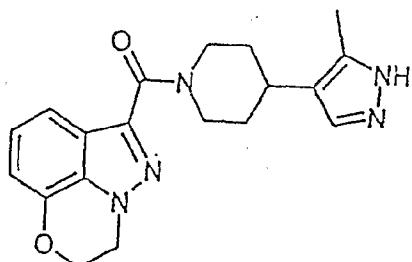
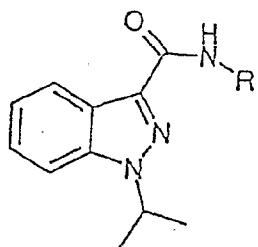


25 e.g. BIMU 1, BIMU 8, DAU 6215, and DAU 6236, are also contemplated.

The carboamides

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are also contemplated.

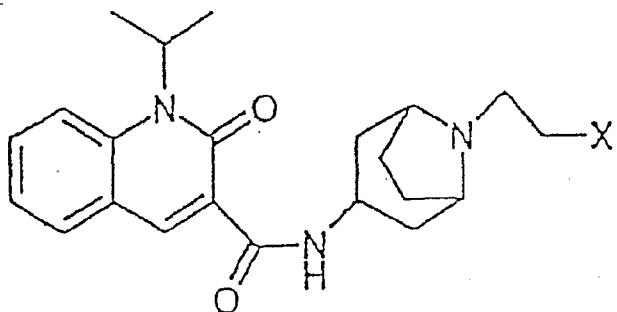
Some indols are also useful as 5-HT₄ agonists, e.g. 5-methoxytryptamine, 2-methylserotonin, and 5-hydroxy-N,N-di-methyltryptamine.

It should be noted that many of these substances may 5 be quaternized on the nitrogen in the side chain without losing the activity.

Benzokinolinones

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According to the present invention, the following compounds can also be used as agonists to the 5-HT₄ receptor: 5-carboxamidotryptamine (5-CT), with the structural formula:

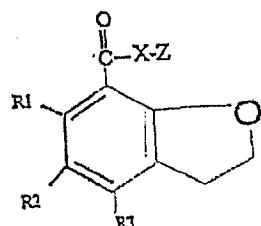
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25 5-HT, 3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α -methyl-5-HT, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxy-30 methyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5. azabicyclo(x.y.z) derivatives,

2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac, 2-[1-(4-piperonyl)piperazinyl]benzothiazole, benz-
5 pyranes,

substituted dihydrobenzofuran derivates with the following structure (see EP 0 766 680)

10.



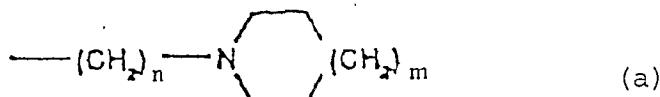
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wherein

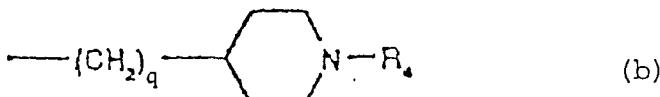
R₁, R₂ and R₃ are, each independently, hydrogen, C₁-C₆ alkyl, halogen, hydroxy, C₁-C₄ alkoxy, amino, C₁-C₄ alkylamino or C₁-C₄ di-alkylamino;
X is O, NH or CH₂;
Z is a group (a), (b), (c) or (d)

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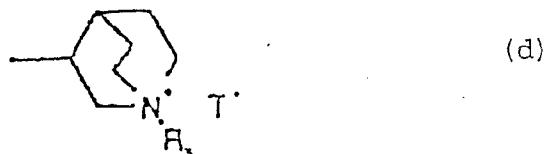


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wherein

15 n is 1, 2, 3 or 4;
 m is zero or 1;
 q is zero, 1 or 2;
 R₄ is hydrogen, C₁-C₆ alkyl, benzyl, cyclohexyl-
 methyl or -CH₂-CH₂-SO₂NH-R₆ in which R₆ is C₁-C₆
 20 alkyl or benzyl;
 R₅ is C₁-C₆ alkyl; and
 T is halogen;
 provided that, when Z is defined under (c), then X
 25 is O or CH₂; or a pharmaceutically acceptable salt
 thereof, for use as a 5-HT₄ receptor agonist.

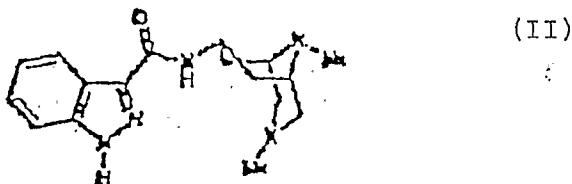
Compounds with the following indazole structure:
 (see JP 08169830)

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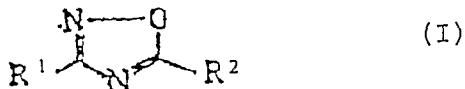
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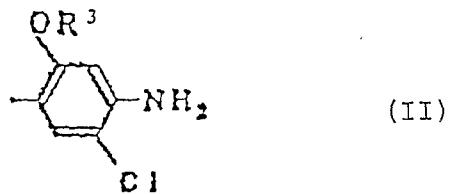


This 5-HT₄ receptor agonist contains a new
 10 diazabicyclo derivative of formula I (R is a 4-6C
 cycloalkyl) or its pharmaceutically permissible salt as
 an active component. The compound of formula I is
 especially preferably N-(endo-3,9-dimethyl-3,9-
 diazabicyclo[3.3.1]non-7-yl)-1-cyclobutylindazol-3-
 15 carboxamide. The 5-HT₄ receptor agonist is especially an
 agent for the y1)-1-cyclobutylindazol-3-carboxamide. The
 5-HT₄ receptor agonist is especially an agent for the
 oxadiazole derivatives (see WO95/32965)

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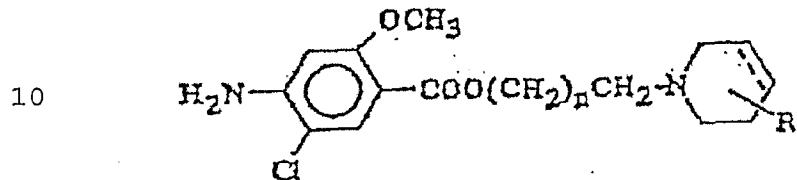
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An oxadiazole derivative represented by general
 formula (I) and useful as a 5-HT₄ receptor agonist, a
 pharmaceutically acceptable salt thereof, or a medicinal
 35 composition thereof wherein one of R1 and R2 represents
 (a) and the other represents -A-Het; A represents a mere
 bond or lower alkylene; Het represents a monocyclic,

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fused or cross-linked heterocyclic group containing at least one nitrogen atom and bonded to A at the ring carbon atom; and R3 represents lower alkyl, lower alkenyl or lower alkynyl.

5 4-amino-5-chloro-2-methoxybenzoic esters (see WO95/25100)



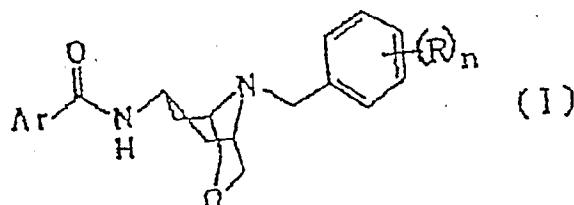
(I)

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wherein n is 1 or 2, R represents a hydrogen or halogen atom or a cyano, hydroxy, (C1-C4)alkyl, (C1-C4)-alkoxy, carboxy, (C1-C4)alkoxycarbonyl, aminocarbonyl, mono(C1-C4)alkylaminocarbonyl, di(C1-C4)alkylamino-carbonyl, mono(C1-C4)alkylamino, di(C1-C4)alkylamino, (C1-C5)alcanoylamino or (C1-C5)alcanoyl group, and when R is a hydrogen atom the dashed line may represent a double bond, as well as pharmaceutically acceptable salts or solvates and quaternary ammonium salts for the preparation of medicaments having 5-HT4 agonistic action.

Oxazabicyclo derivatives (see EP 0 623 621)

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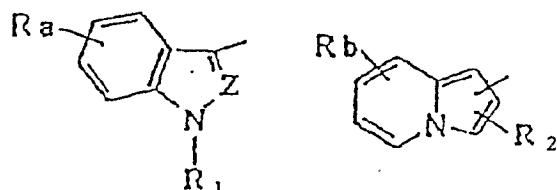
wherein R is a hydrogen atom, a halogen atom, a halo(C1-C6)alkyl group, a (C1-C6)alkoxy group, a nitro group, a hydroxyl group or an amino group, n

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is 1 or 2, the R groups being the same or different when n is 2, and Ar represents a radical of formula (II), (III), (IV), (V), (VI), (VII) or (VIII)

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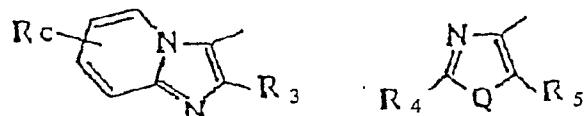


(II)

(III)

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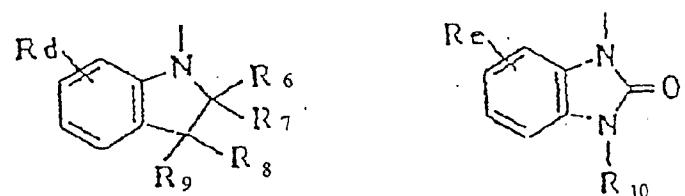


(IV)

(V)

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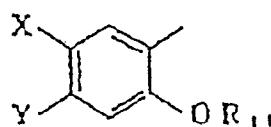


(VI)

(VII)

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14



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(VIII)

wherein

R_a to R_e are independently a hydrogen atom, a halogen atom, a hydroxyl group, a (C₁-C₆)alkoxy group or a (C₁-C₈)alkyl group;

10 R₁ is a hydrogen atom, a (C₁-C₈)alkyl group, a (C₃-C₈)alkenyl group, a (C₃-C₈)alkynyl group, a (C₃-C₆)cycloalkyl group, a (C₃-C₆)cycloalkyl(C₁-C₆)-alkyl group, a (C₁-C₆)alkoxy(C₂-C₅)alkyl group, a (C₃-C₆)oxoalkyl group, a (C₁-C₆)alkoxycarbonyl-(C₁-C₆)alkyl group, a (C₁-C₆)alkoxycarbonyl group, a (C₁-C₆)alkanoyl group, a di(C₁-C₆)alkylamino(C₂-C₆)-alkyl group, a hydroxy(C₂-C₆)alkyl group, a halo(C₁-C₆)alkyl group, a cyano(C₁-C₆)alkyl group, 4,6-diamino-2-triazenylmethyl group or a benzyl group

15 optionally substituted by one or two substituents selected from the group consisting of halogen, (C₁-C₆)alkoxy, nitro, hydroxyl and amino;

Z is CH or N;

20 R₂, R₃, R₅, R₆, R₉, R₁₀ and R₁₁ are independently a hydrogen atom or a (C₁-C₆)alkyl group;

25 R₄ is a (C₁-C₆)alkyl group, a pyridyl group or a phenyl group optionally substituted by halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy or trifluoromethyl;

Q is N, S or O;

30 X is a halogen atom;

Y is NH₂ or a phthalimido group;

R₇ is a hydrogen atom;

R₈ is a hydrogen atom or a (C₁-C₄)alkyl group; or R₇ and R₈ together form a single bond.

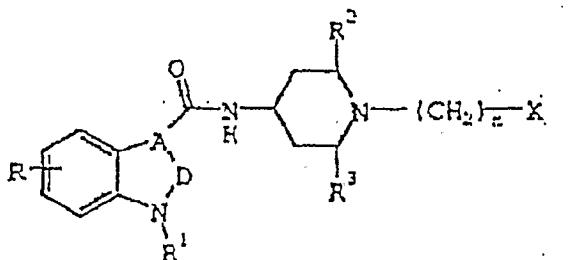
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Compounds having the following structure (see

EP 0 908 459)

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I;

wherein

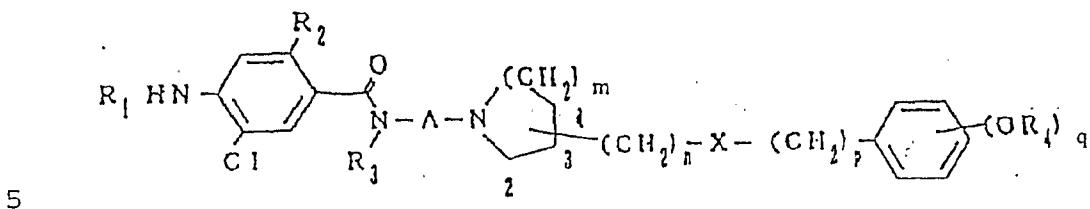
A-D is C=N or N-C=O;

10 n is 1, 2, 3, 4 or 5;

R is hydrogen, halo, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthio, cyano, trifluoromethyl, carboxamido, mono or di(C₁-C₄ alkyl) carboxamido;15 R¹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or substituted C₃-C₆ cycloalkyl;R² and R³ are each hydrogen or taken together form a bridge of 1 to 4 methylene units;X is OR⁴ or NR⁴R⁵;20 R⁴ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, phenyl, substituted phenyl, (C₁-C₆ alkyl)CO, benzoyl, substituted benzoyl, tricyclo[3.3.1.1^{3,7}]decan-1-oyl, or S(O)₂R⁶;25 R⁵ is hydrogen or R⁴ and R⁵ together with the nitrogen to which they are attached form a 1-pyrrolidinyl, 1-piperazinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 2,3-dihydro-1-indolinyl, 4-morpholinyl, 1-piperidinyl, 1-hexamethyleneiminyl, or phthalimidyl ring;30 R⁶ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, phenyl, or substituted phenyl; or a pharmaceutically acceptable salt thereof.

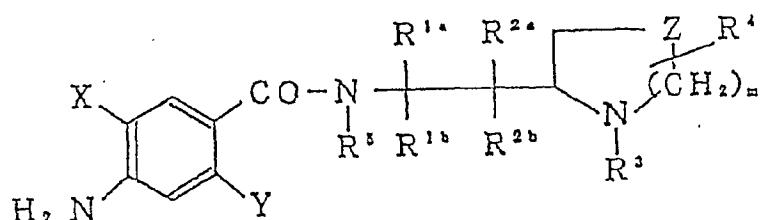
35 Benzamide derivatives having the following structures

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having the substituents specified in WO 97/10207

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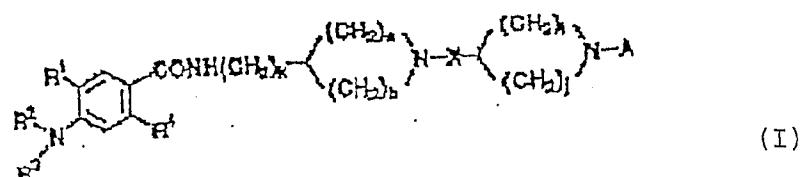


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having the substituents specified in WO95/18104.

and

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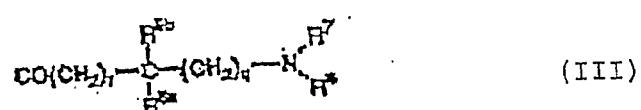
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(see JP11001472)

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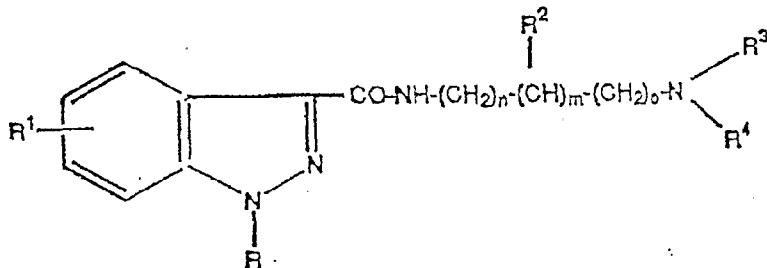


This novel compound is represented by formula I. [R¹ is a halogen; R² is H, a lower alkyl; R³ is H, a lower alkyl, a lower alkanoyl; R⁴ is a lower alkoxy; a is 1 or 2; b is 2 or 3; i is 1 or 2; j is 2 or 3; k is 0, 1, 2; X is -(CH₂)_m- (m is 1 or 2); A is a group of formula II or formula III (p is 1, 2, 3; q is 0, 1, 2, 3; r is 0, 1, 2; R^{5a} is H, a lower alkyl; R^{5b} is H, a lower alkyl)], typically 4-amino-N-[1-[1-(3-aminopropyl)-4-piperidinyl-methyl]-5-chloro-2-methoxybenzamide.

10

Indazolecarboxamides (see WO 96/33713)

15



20

wherein:

R is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl;R¹ is hydrogen, halo, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy or alkylthio, cyano, trifluoromethyl,25 carboxamido, mono- or di(C₁-C₄ alkyl)carboxamido; m, n and o are independently 0-5, provided that the sum of m, n and o is 2-5;R² is hydrogen or C₁-C₄ alkyl;30 R³ and R⁴ combine with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperazinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 2,3-dihydro-1-indolinyl, 4-morpholinyl, 1-piperidinyl or 1-hexamethyleneiminy, substituted with phenyl,naphthyl, (phenyl or naphthyl)(C₁-C₃ alkyl), (phenyl or naphthyl)(C₁-C₃ alkanoyl), amino, mono- or35 di(C₄-C₄ alkyl)amino, or a group of the formula -NH-Y-R⁵; provided that a piperazinyl or morpholinyl

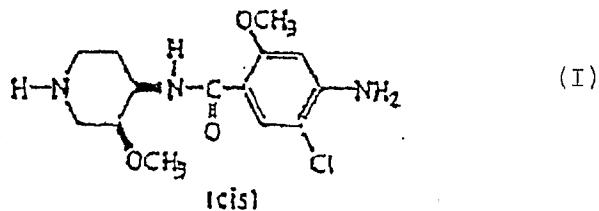
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group may not be substituted with amino, mono- or di(C₁-C₄ alkyl)amino, or -NH-Y-R⁵;
 wherein a phenyl or naphthyl group is unsubstituted or substituted with 1-3 halo, C₁-C₃ alkyl or C₁-C₃ alkoxy groups;
 5 Y is carbonyl, sulfonyl, aminocarbonyl or oxycarbonyl;

(+)-norcisapride of formula (I) and compounds (V), and
 10 its pharmaceutically acceptable acid additions salts;
 compounds of formula (V), wherein the piperidine ring has the absolute configuration (3S, 4R) and PG is
 methyloxycarbonyl, ethyloxycarbonyl, tert-
 butyloxycarbonyl or phenylmethyl. (see WO 99/02496)

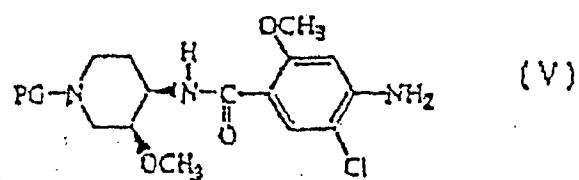
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Thiophene carboxamide, 5-HT4 agonist

Synthesis of thiophene carboxamide derivatives as serotonin 5-HT4 receptor agonists. Monge A, Palop J,
 5 Pérez S, Oset C, Lasheras B; Farmaco 1997 Feb, 52:2:89-92.

New thiophene carboxamide derivatives 3(a-j) were synthesized as serotonin 5-HT4 receptor agonists.
 10 Preliminary results showed that the compounds 3a, 3d, 3e and 3f caused concentration dependent relaxation of carbachol-induced contraction in tunica muscularis mucosae in rat oesophagus.

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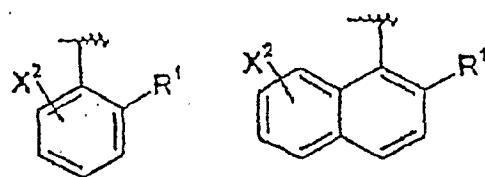
(I)

EP 0 957 099 A2

or the pharmaceutically acceptable salt thereof,
 20 wherein

Z is oxygen, S(O)_m wherein m is 0, 1 or 2; or NQ wherein Q is hydrogen, (C₁-C₆)alkyl or phenyl;
 25 X is hydrogen, chloro, fluoro, bromo, iodo, hydroxy, nitro, cyano, (C₁-C₆)alkyl, trifluoromethyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl S(O)_a wherein a is 0, 1 or 2; or phenyl wherein the phenyl group is optionally substituted by hydrogen, halo, hydroxy, nitro, cyano, (C₁-C₆)alkyl, trifluoromethyl, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl S(O)_b wherein b is 0, 1 or 2;
 30 Y is

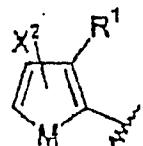
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or

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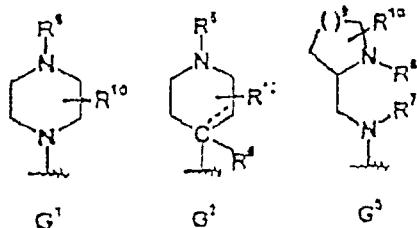


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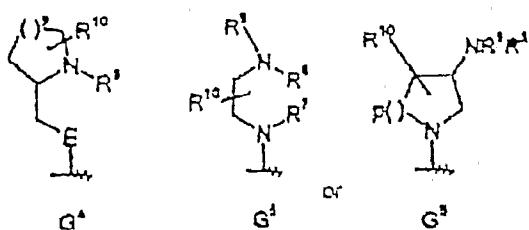
wherein M is oxygen or sulfur;
 X² is hydrogen, fluoro, chloro, trifluoromethyl,
 (C₁-C₆)alkyl, (C₁-C₆)alkoxy or (C₁-C₆)alkyl S(O)_c
 wherein c is 0, 1 or 2;
 R¹ is a group of formulas

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20



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wherein the broken line represents an optional double bond;

35

p is 1, 2 or 3;
 E is oxygen or S(O)_d wherein d is 0, 1 or 2;

R⁸ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl optionally substituted with (C₁-C₆)alkoxy or one to three fluorine atoms, or [(C₁-C₄)alkyl]aryl wherein the aryl moiety is phenyl, naphthyl, or heteroaryl (CH₂)_q-, wherein the heteroaryl moiety is selected from the group consisting of pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl and benzisothiazolyl and q is zero, one, two, three or four, and wherein said aryl and heteroaryl moieties may optionally be substituted with one or more substituents independently selected from the group consisting of chloro, fluoro, bromo, iodo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano and (C₁-C₆)alkyl S(O)_e wherein e is 0, 1 or 2;

10 R⁷ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, [(C₁-C₄)alkyl]aryl wherein the aryl moiety is phenyl, naphthyl, or heteroaryl-(CH₂)_r-, wherein the heteroaryl moiety is selected from the group consisting of pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl and benzothiazolyl and r is zero, one, two, three or four, and wherein said aryl and heteroaryl moieties may optionally be substituted with one or more substituents independently selected from the group consisting of chloro, fluoro, bromo, iodo, (C₁-C₆)-alkyl, (C₁-C₆)alkoxy, trifluoromethyl, -C(=O)-(C₁-C₆)alkyl, cyano and (C₁-C₆)alkyl S(O)_f, wherein f is 0, 1 or 2;

15 or R⁶ and R⁷ taken together form a 2 to 4 carbon chain;

20 R⁸ is hydrogen or (C₁-C₃)alkyl;

25 R⁹ is hydrogen or (C₁-C₆)alkyl;

30 or R⁸ and R⁹, together with the nitrogen atom to which they are attached, form a 5 to 7 membered heteroalkyl ring that may contain from zero to four heteroatoms selected from nitrogen, sulfur and oxygen;

R^{10} is hydrogen or (C_1-C_6) alkyl;
 R^2 is hydrogen, (C_1-C_4) alkyl, phenyl or naphthyl,
wherein said phenyl or naphthyl may optionally be
substituted with one or more substituents
5 independently selected from chloro, fluoro, bromo,
iodo, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl,
cyano and (C_1-C_6) alkyl $S(O)_g$ wherein g is 0, 1 or 2;
and
 R^3 is $-(CH_2)_tB$, wherein t is zero, one, two or three
10 and B is hydrogen, phenyl, naphthyl or a 5 or 6
membered heteroaryl group containing from one to
four heteroatoms in the ring, and wherein each of
the foregoing phenyl, naphthyl and heteroaryl groups
may optionally be substituted with one or more
15 substituents independently selected from chloro,
fluoro, bromo, iodo, (C_1-C_6) alkyl, (C_1-C_6) alkoxy,
 (C_1-C_6) alkoxy- (C_1-C_6) alkyl, trifluoromethyl,
trifluoromethoxy, cyano, hydroxy, COOH and $(C_1-$
 $C_8)$ alkyl $S(O)_h$ wherein h is 0, 1 or 2.

Piperazinyl benzothiazole, 5-HT4 agonist

VB20B7, a novel 5-HT-ergic agent with gastrokinetic
5 activity. I. Interaction with 5-HT3 and 5-HT4 receptors.
Ramirez MJ, Garcia-Garayoa E, Romero G, Monge A, Roca J,
Del Rio J, Lasheras B J Pharm Pharmacol 1997 Jan,
49:1:58-65.

10 This study describes the in-vitro interaction of the
gastrokinetic agent 2[1-(4-piperonyl)piperazinyl]-
benzothiazole (VB20B7) with the 5-hydroxytryptamine
5-HT3 and 5-HT4 receptor subtypes, using functional
as well as radioligand binding studies. The
15 benzamide derivative cisapride was used as a
comparison. In radioligand binding assays VB20B7
showed, like cisapride, a weak affinity at 5-HT3
receptors from rat cerebral cortex. The new compound
lacked any affinity at other 5-HT receptors or at
20 dopaminergic D2 receptors, whereas cisapride showed
high affinity for the 5-HT4 receptors from guinea-
pig hippocampus and moderate affinity at
dopaminergic D2 receptors. In the non-stimulated
guinea-pig ileum, the concentration-response curves
25 to the specific 5-HT3 agonist 2-Me-5-HT and to 5-HT
were shifted to the right by VB20B7. In the rat
oesophagus tunica muscularis mucosae preparation
(TMM), VB20B7 was evaluated for its activity at 5-
HT4 receptors. VB20B7 behaved as a 5-HT4 receptor
30 agonist, inducing a concentration-dependent
relaxation of the preparation precontracted with
carbachol. In this preparation, VB20B7 and cisapride
were able to stimulate adenylate cyclase activity,
an effect probably mediated through activation of 5-
35 HT4 receptors, as can be inferred from the blockade
by the 5-HT4 antagonist, tropisetron, of the
enhanced cAMP formation. However, consistent with

the lack of affinity at central 5-HT4 receptors, VB20B7 did not stimulate cAMP formation in guinea-pig hippocampal slices. VB20B7 also caused an increase in the twitch response of the transmurally stimulated guinea-pig ileum, although at a concentration higher than cisapride. This effect was blocked by desensitisation of the 5-HT4 receptor with 5-MeOT and also by the 5-HT4 receptor antagonist tropisetron. Both VB20B7 and cisapride increased the K(+) evoked acetylcholine release in this preparation. The results show that VB20B7 possesses affinity for 5-HT4 receptors located in the rat TMM and guinea-pig ileum preparations, but is devoid of affinity at central 5-HT4 receptors. In addition, VB20B7 shows low to moderate affinity at both central and peripheral (enteric) 5-HT3 receptors. The interaction of VB20B7 with the peripheral 5-HT4 and 5-HT3 receptors may be relevant for the gastrokinetic effects of the new compound.

20

VA21B7 (3-[2-(4'-piperonylpiperazinyl)indolyl]-caboxaldehyde). The pharmacology of VA21B7: an atypical 5-HT3 receptor antagonist with anxiolytic-like properties in animal models. Artaiz I, Romero G, Zazpe A, Monge A, Calderó JM, Roca J, Lasheñas B, Del Río J Psychopharmacology (Berl) 1995 Jan, 117:2:137-48.

WO 95/32965

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2-[4-[3-(4-aryl/heteroaryl-1-piperazineyl)propoxy]phenyl]-2H-benzotriazoles and their N-oxides as ligands for serotonergic and dopamine receptors., Sparatore A, Goegan M, Cagnotto A, Sparatore F; Farmaco 1999 Jun 30, 54:6:402-10.

35

A small set of 2-4-[3-(4-aryl/heteroaryl-piperazinyl)propoxy]phenyl-2H-benzo tri azoles and corresponding N-oxides were prepared. The synthesized compounds were able to bind on some serotonin (5-HT1A, 5-HT2A) and dopamine (D2, D3) receptors, while displaying poor or no affinity for 5-HT1B, 5-HT2C, 5-HT3 and 5-HT4 subtypes. The strong contribution of the N-oxide function for the binding on 5-HT1A, D2 and D3 receptors is noteworthy. For 2-4-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propoxy]phenyl-2H-benzotriazole-1-oxide (4b), the binding constants (Ki) were 11.9 (5-HT1A) and 10.5 nM (D3). In a general pharmacological screening, the 2-4-[3-(4-phenyl-1-piperazinyl)propoxy]phenyl-2H-benzotriazole (3a) exhibited only very weak activities, with the exception of protecting mice from cyanide-induced hypoxia.

Arylcarbamates

Arylcarbamate derivatives of 1-piperidineethanol as potent ligands for 5-HT4 receptors. Soulier JL, Yang D, Brémont B, Croci T, Guzzi U, Langlois M; J Med Chem 1997 May 23, 40:11:1755-61.

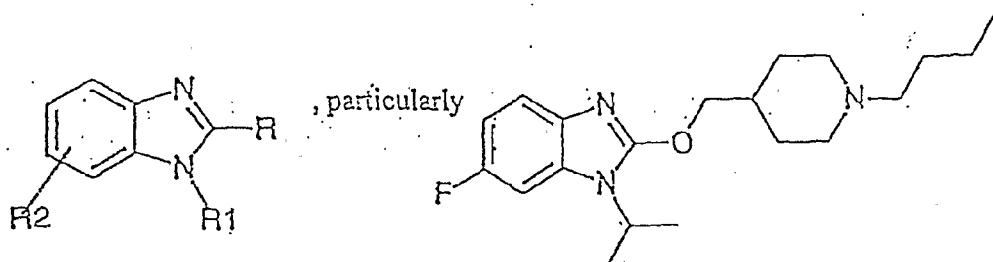
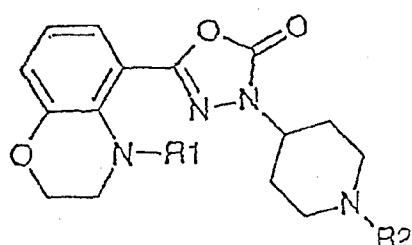
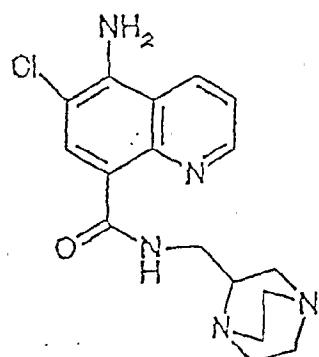
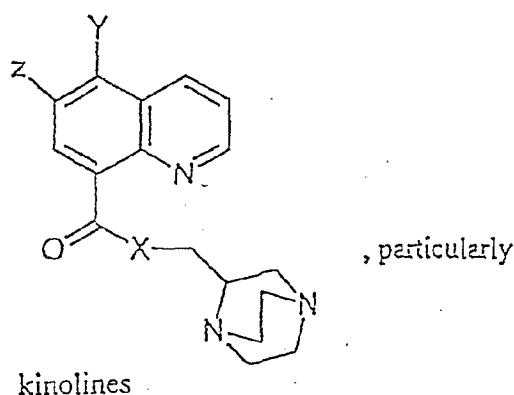
A series of carbamate derivatives (7) of 2-(1-piperidinyl)ethyl 4-amino-5-chloro-2-methoxybenzoates, which have been described as potent agonists and antagonists of 5-HT4 receptors, were synthesized. They were evaluated using radioligand binding assays with [³H]GR 113808, a 5-HT4 receptor selective ligand, in the rat striatum and the electrically stimulated myenteric plexus longitudinal muscle of the guinea pig. In contrast to the previously described ester derivatives, a drop in the affinity for 5-HT4 receptors was observed and the compounds were inactive as agonists in the guinea pig ileum.

preparation. Unexpectedly, the ortho-substituted carbamates 8b,c (R' =H, RO=MeO or EtO, R''=H) had nanomolar affinity for 5-HT4 receptors (Ki = 8.9 +/- 0.5 and 2.6 +/- 0.4 nM, respectively). As reported 5 previously, the cis- or trans-3,5-dimethyl substitution of piperidine (8n,o) was particularly favorable (Ki = 1.1 +/- 0.6 nM for both isomers). 8c is an antagonist equipotent to the 5-HT4 receptor antagonist SDZ 205-557 (1).

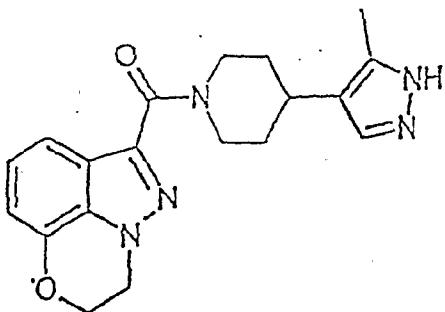
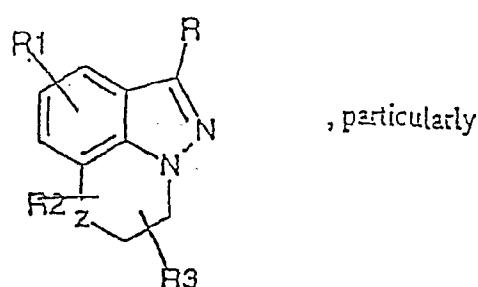
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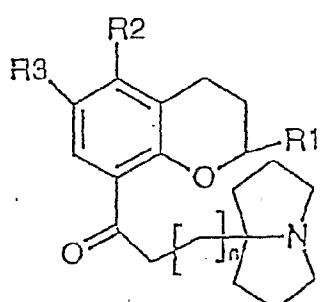
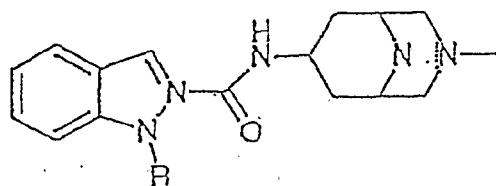
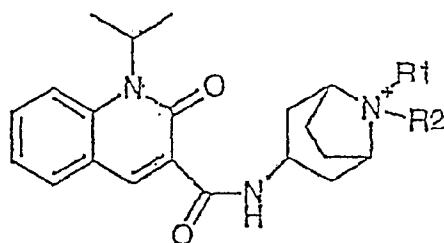
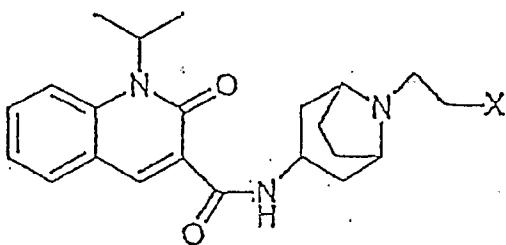
The most interesting 5-HT₄ receptor agonists for the present indications are VB20B7, RS67333, BIMU 1, BIMU 8, 5-methoxytryptamine, Zucopride, RS56532, Mosapride, Pancopride, Itasetron, BRL 24924, and SC 53116.

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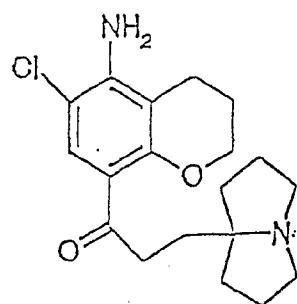
Further 5-HT4 agonist structures useful according to the present invention2-piperidinmethylethers
of bensimidazoloxadiazalon based
substance

kinolines

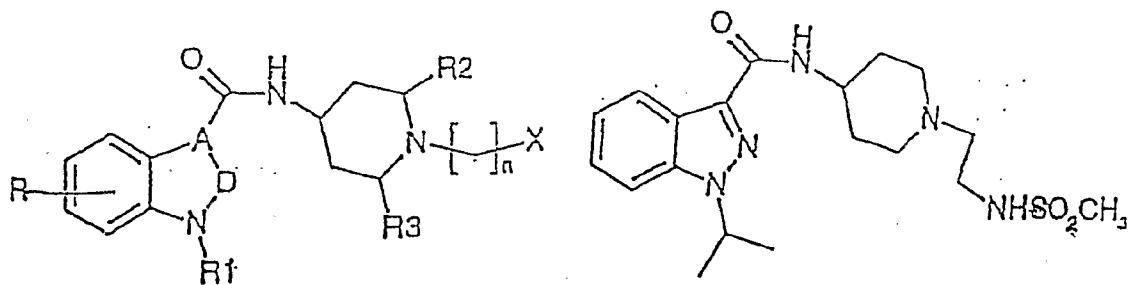




, particularly



benzopyranes.



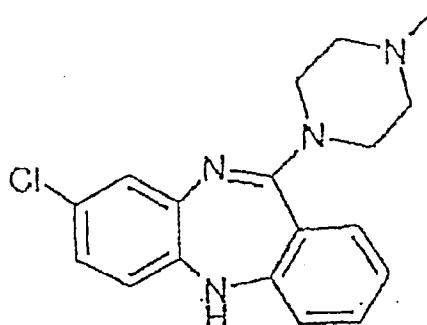
The most preferred 5-HT₄ receptor agonist is RS 67333.

According to the present invention, several known 5-HT₃ antagonist compounds are, unexpectedly, able to enhance a 5-HT-induced airway relaxation. The 5-HT₃ receptor is a ligand modulated ion channel. Several potent and specific 5-HT₃ antagonists exist today, of which ondansetron, tropisetron, granisetron, and dolasetron are commercial pharmaceuticals, but not against disorders involving airway constriction.

Some of the 5-HT₃ receptor antagonists are at the same time 5-HT₄ receptor agonists. However, for a substance to be active as a 5-HT₃ receptor antagonist, the distance from the aromatic center to the basic nitrogen should be about 7,5 Å and no large substituents are tolerated on the basic nitrogen. In contrast, for 5-HT₄ receptor agonists the corresponding distance is about 8 Å, and a large lipophilic group may be bound to the basic nitrogen, thereby obtaining a better binding to 5-HT₄.

The 5-HT₃ antagonists may be divided into certain classes on the basis of chemical structure. Some are unspecific, e.g.

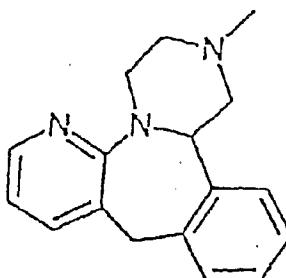
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benzazepines, e.g. mirtazapine

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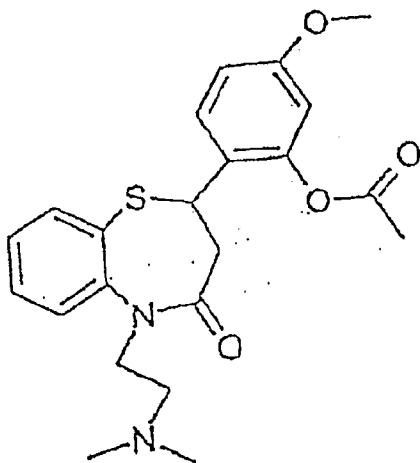


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benztiazepines, e.g. diltiazem

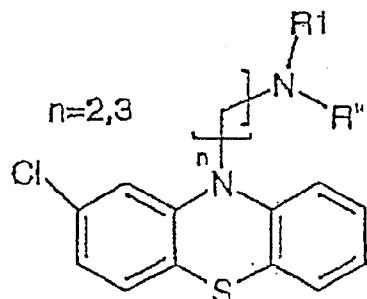
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15 and fentiazines

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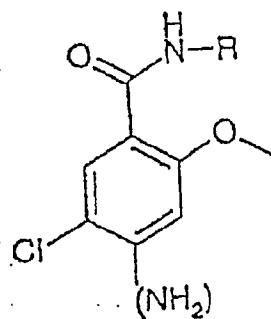
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e.g. perphenazine, chlorpromazine, stemetil.

Some are 5-HT4 agonists, e.g. benzamides

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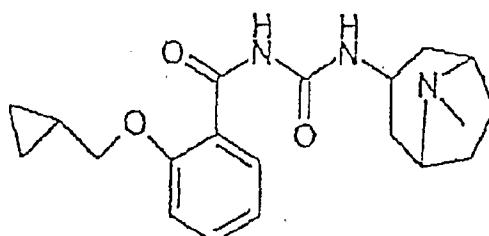


(cisapride, zacopride,
mosapride, metoclo-
pramide, pancropride,
BRL 24924, BMY 33462)

31

and

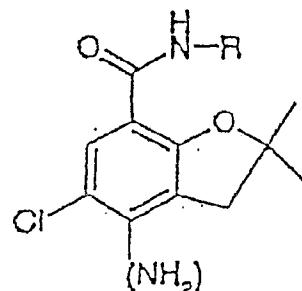
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WAY 100289

10 2,3-dihydro-benzofuran-7-carboxamides

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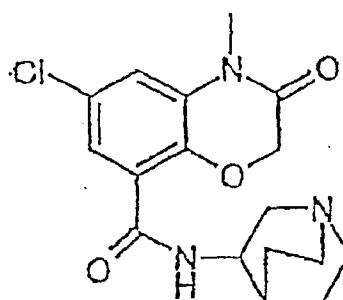


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(e.g. zatosetron=LY 277359, ADR 851);

1,4-bensoxazin-8-carboxamides

25

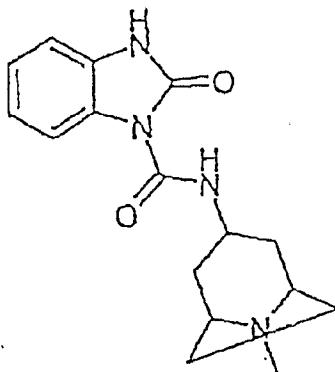


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e.g. azasetron (=Y25130)

benzimidazolones

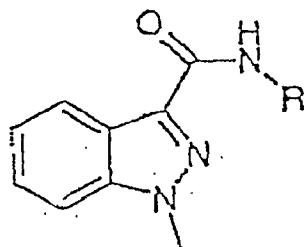
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e.g. itasetron (=DAU 6215);
 indazol-3-carboxamides

15

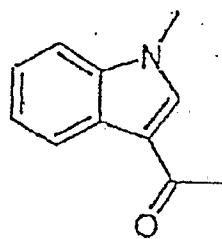


20

e.g. N 3389, LY 278584, DAT 582

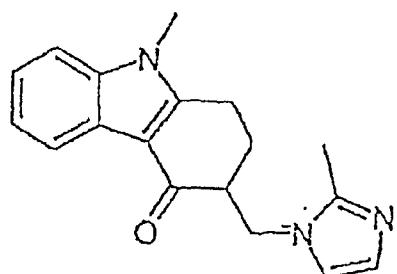
25 The latter group reminds most of the specific 5-HT₃ antagonists, which contains the group

30



in different forms, such as

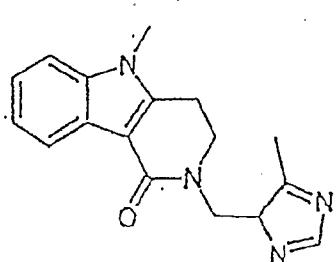
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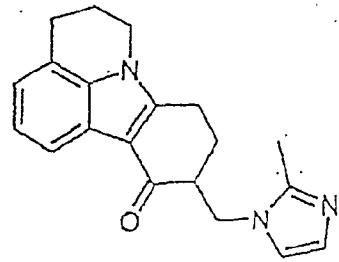
ondansetron

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alosetron

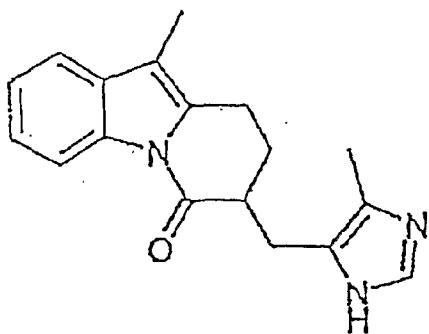


cilansetron

In one group of substances the structure has been
 20 inverted and the carbonyl group has been placed on the
 indoline nitrogen

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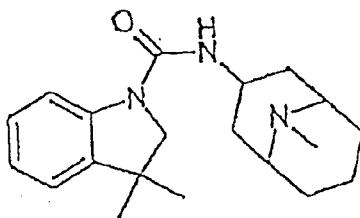


FK 1052

This substance is unique by being an antagonist
 against both 5-HT₃ and 5-HT₄ receptors.

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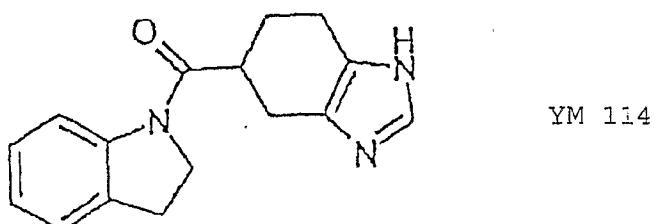
BRL 46470 A

BRL 46470A binds to two different positions of the receptor.

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A further development is the so-called bisindoles

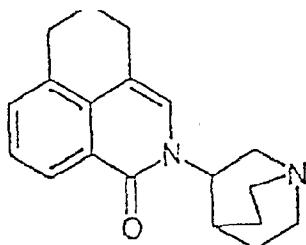
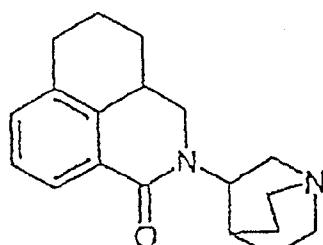
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YM 114

Another group is the isoquinoline-1-ones

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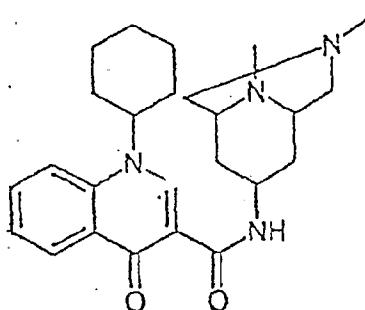
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palonosetron (=RS 25259-197)

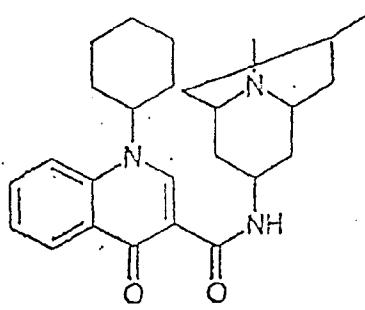
RS 42358-197

and the quinoline-3-carboxamides

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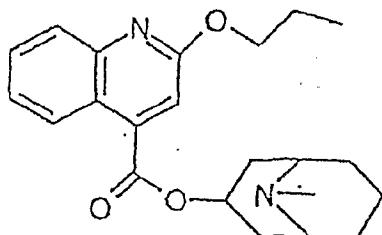
WAY-SEC 579

Mirisetron (=WAY 100579)

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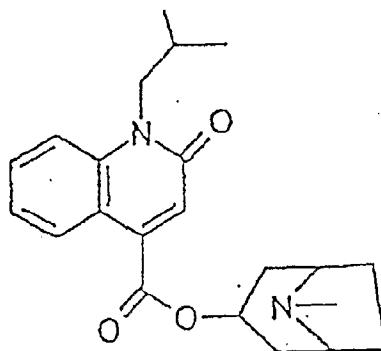
Also the quinoline-4-carboxylates are active antagonists

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10 e.g. KF 17643

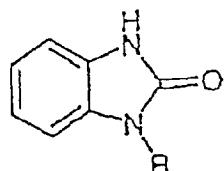
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20 e.g. KF 18259

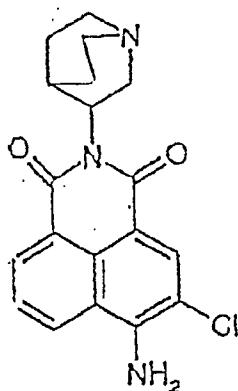
Other compounds are benzimidazolones

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e.g. droperidol (neurolidol, etc.), itasetron (DAU6215) and the naphthimides

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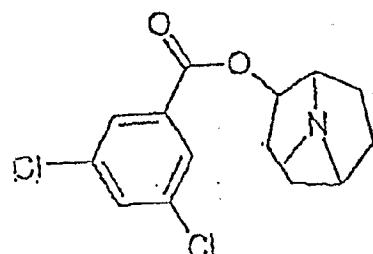
RS 56532

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e.g. RS 56532

A unique single structure is MDL 72222, which also is a specific 5-HT₃ antagonist

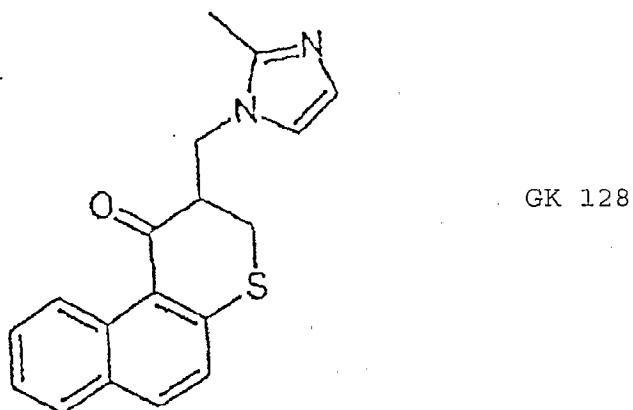
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Other specific structures are

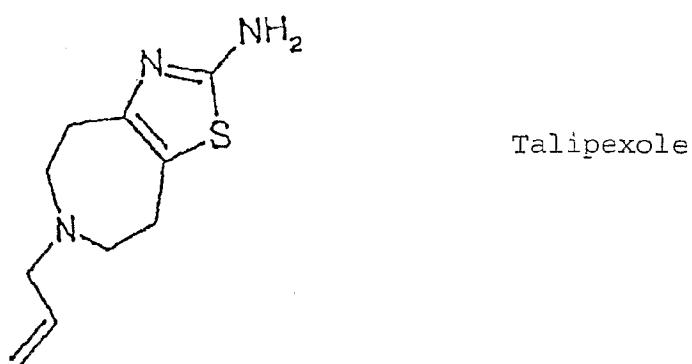
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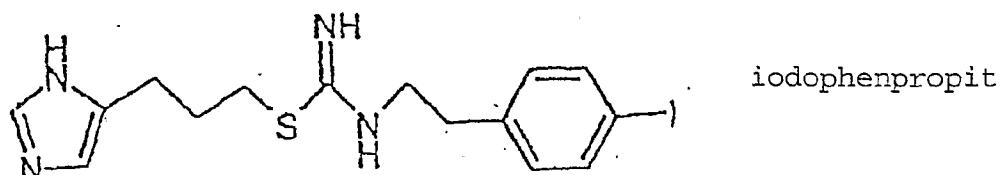
GK 128

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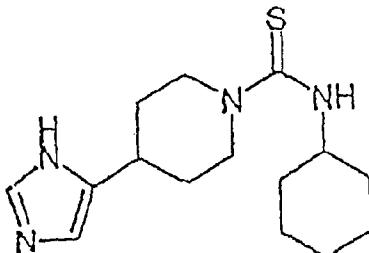
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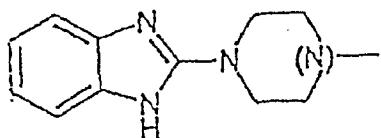
iodophenpropit

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thioperamide, and

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2-piperidin- and 2-piperazin-
benzimidazoles.

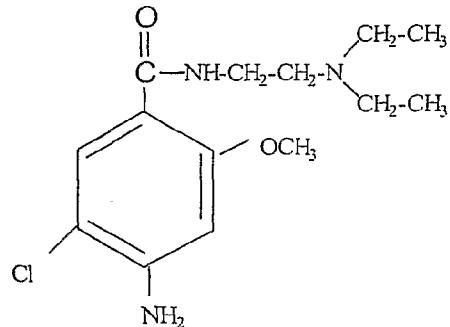
According to the present invention, the following compounds can also be used as antagonists to the 5-HT₃ receptor: (R)-zacopride, 2-methyl-5HT, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyp-roheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYK1-48903, ICS 205-930, Imipramine, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Methysergide, Mianserin, MK 212, N-3256, NAN-190, N-methylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Pancopride, Phenylbiguanide, Pitozifen, Prochlorperazine, QICS 205-930, R(+) zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792,

SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperazine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, 5 Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, Bemesetron, L-683,877, LY-278,584 maleate and pharmaceutically acceptable salts thereof 10 with the same or essentially the same relaxation enhancing effect.

In the following, an alternative presentation of useful compounds according to the present invention and references thereto is listed.

15 N-substituted benzamides

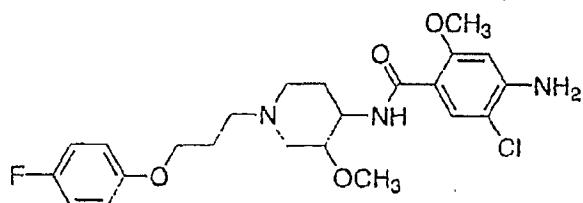
- Metoclopramide



20 • QX 222. The compound is an analogue to lidocain®, which is a N-substituted benzamide derivative.

25 • Cisapride (Cizapride) cis-4-Amino-N- [1- [3- (p-fluorophenoxy) propyl] -3-methoxy-4-piperidyl] -5-chloro-o-anisamide. The compound is also a known 5-HT4 agonist.

cis-4-Amino-N-[1-[3-(*p*-fluorofenoxi)propyl]-3-metoxi-4-piperidyl]-5-kloro-*o*-anisamid



- Pancopride (((+)-N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-amino-5-chlorobenzamide)
Pancopride, a potent and long-acting 5-HT3 receptor antagonist, is orally effective against anticancer drug-evoked emesis., Fernández AG, Puig J, Beleta J, Doménech T, Bou J, Berga P, Gristwood RW, Roberts DJ; *Eur J Pharmacol* 1992 Nov 10, 222:2-3:257-64

10 Pancopride (((+)-N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-amino-5-chlorobenzamide), is a new potent and selective 5-HT3 receptor antagonist, orally and parenterally effective against cytotoxic drug-induced emesis. In vitro, pancopride displayed high affinity ($K_i = 0.40$ nM) for [3 H]GR65630-
15 labelled 5-HT3 recognition sites in membranes from the cortex of rat brains. In vivo, pancopride antagonized 5-HT-induced bradycardia in anaesthetized rats when administered i.v. 5 min
20 (ID₅₀ = 0.56 microgram/kg) or p.o. 60 min (ID₅₀ = 8.7 micrograms/kg) before 5-HT challenge. A single oral dose (10 micrograms/kg) of pancopride produced a significant inhibition of the bradycardic reflex

over an 8-h period. Pancopride dose dependently inhibited the number of vomiting episodes and delayed the onset of vomiting induced by cisplatin in dogs (ID₅₀ = 3.6 micrograms/kg i.v. and 7.1 micrograms/kg p.o.). Pancopride was also effective in blocking mechlorethamine- and dacarbazine-induced emesis. Unlike metoclopramide, pancopride was shown to lack any measurable antidopaminergic activity both in vitro and in vivo. These results support clinical data, indicating that pancopride will be a useful drug for treating cytostatic-induced emesis in humans.

- (R)-zacopride (R+ zacopride, zacopride) IUPAC name: 4-amino-N-(1-azabicyclo[2.2.2] oct-3yl)-5-chloro-2-methoxy-benzamide.
The differential activities of R (+)- and S(-)-zacopride as 5-HT₃ receptor antagonists.
Barnes JM, Barnes NM, Costall B, Domeney AM, Johnson DN, Kelly ME, Munson HR, Naylor RJ, Young R; Pharmacol Biochem Behav 1990 Dec, 37:4:717-27

R (+)- and S(-)-zacopride were assessed as potential 5-HT₃ receptor antagonists in behavioural and biochemical tests. The S(-)isomer was more potent than the R(+)isomer to antagonise the hyperactivity induced by the injection of amphetamine or the infusion of dopamine into the nucleus accumbens in the rat. In contrast, the R(+)isomer was more potent to reduce the aversive behaviour of mice to a brightly illuminated environment and in a marmoset human threat test, to facilitate social interaction in rats, to increase performance in a mouse habituation test and prevent a scopolamine-induced impairment, and to antagonise the inhibitory effect of 2-methyl-5-hydroxytryptamine to reduce [³H]acetylcholine release in slices of the rat

5 entorhinal cortex. In binding assays, [³H]S(-)-zacopride and [³H]R(+) -zacopride labelled homogenous populations of high-affinity binding sites in the rat entorhinal cortex, R(+) -zacopride compete for a further 10 to 20% of the binding of [³H]R(+) /S(-)-zacopride or [³H]R(+) -zacopride in excess of that 10 competed for by (S) (-)-zacopride. It is concluded that both isomers of zacopride have potent but different pharmacological activities, with the possibility of different recognition sites to mediate their effects.

- BRL 24682

15 The compound is also a known 5-HT₄ agonist.

- BRL 24924

15 [(+/-) - (endo)] -4-amino-5-chloro-2-methoxy-N- (1-azabicyclo- [3.3.1] -non- 4-yl) benzamide hydrochloride. The compound is also a known 5-HT₄ 20 agonist.

- Mosapride ((4-amino-5-chloro-2-ethoxy-N- [[4- (4-fluorobenzyl) -2-morpholinyl]methyl] benzamide citrate.

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- Renzapride= BRL 24924; see above

- SC-52491 (Azanoradadamantane)

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- SC-53116 ((1-S,8-S) -4-amino-5-chloro-N- [(hexahydro-1H-pyrrolizin-1-yl) methyl]-2-methoxy-benzamide hydrochloride)

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- Batanopride (4-amino-5-chloro-N- [2-(diethylamino)ethyl]2-(1-methyl-2-oxopropoxy) benzamide). Batanopride is also known by the name BMY-25801.

- WAY 100289

Indoles, Indole-1-carboxamides and Imidazole dérivatifs

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- 2-methyl-5-HT
- 5,7-DHT= 5,7-dihydroxy-tryptamine

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- Bisindoles

- Bufotenine = (5-hydroxy-N,N-dimethyltryptamine)

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- BRL 46470A (endo-N- (8-methyl-8-azabicyclo [3.2.1]oct-3-yl)2,3-dihydro-3,3 dimethyl-indole-1-carboxamide, hydrochloride)

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- BRL 46470 (endo-N- (8-methyl-8-azabicyclo [3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl)

- BRL 47204

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- FK 1052 ((+)-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride)

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Pharmacological characterization of FK1052, a dihydropyridoindole derivative, as a new serotonin 3 and 4 dual receptor antagonist., Nagakura Y, Kadowaki M, Tokoro K, Tomoi M, Mori J, Kohsaka M; Pharmacol Exp Ther 1993 May, 265:2:752-8

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(+)-8,9-Dihydro-10-dihydro-10-methyl-7-[(5-methyl-4-imidazolyl) methyl]pyrido-[1,2-a]indol-6(7H)-one hydrochloride (FK1052) is a newly designed and synthesized 5-hydroxytryptamine (5-HT)3 receptor

antagonist with 5-HT4 receptor antagonistic activity. This compound, as well as ondansetron and granisetron, dose-dependently inhibited the von Bezold-Jarish reflex, a 5-HT3 receptor-mediated response, after intravenous (i.v.) and intraduodenal (i.d.) dosing to rats. The ID50 values showed FK1052 (0.28 microgram/kg, i.v., 5.23 micrograms/kg, i.d.) to be more potent than ondansetron (5.23 micrograms/kg, i.v., 170 micrograms/kg, i.d.) and granisetron (0.70 micrograms/kg, i.v., 66 micrograms/kg, i.d.). Furthermore, bioavailabilities of the test drugs by ID50 ratio (i.d./i.v.) showed that FK1052 (17) was better absorbed than ondansetron (33) and granisetron (94) and possessed a similar duration of action to that of ondansetron and granisetron. We also examined the effects on 2-methyl-5-HT-, 5-HT- and 5-methoxytryptamine-induced contractions of guinea pig isolated ileum. FK1052, ondansetron and granisetron concentration-dependently inhibited 2-methyl-5-HT, a 5-HT3 agonist-induced contraction. The pA2 values for the 5-HT3 receptor indicated that FK1052 (6.36) was 40 times and three times more potent than ondansetron (6.79) and granisetron (7.86), respectively. FK1052, unlike ondansetron and granisetron, inhibited the 5-HT4-mediated component of concentration-response curve to 5-HT. Furthermore, FK1052 suppressed 5-methoxytryptamine, a 5-HT4 agonist-induced contraction in a concentration-dependent but insurmountable manner.

- RU 24969 (5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)-1 H-indole)
- SDZ 206-792

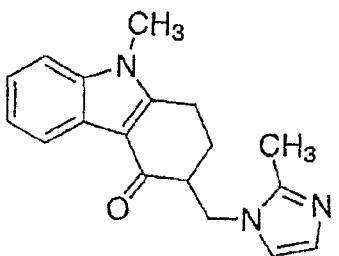
Characterisation of 5-HT3 recognition sites in membranes of NG 108-15 neuroblastoma-glioma cells with [³H]ICS 205-930. Neijt HC, Karpf A, Schoeffter P, Engel G, Hoyer D *Naunyn Schmiedebergs Arch Pharmacol* 1988 May, 337:5:493-9

1. The binding characteristics of [³H]ICS 205-930, a potent and selective 5-hydroxytryptamine 5-HT3 receptor antagonist, were investigated in membranes prepared from murine neuroblastoma-glioma NG 108-15 cells. 2. [³H]ICS 205-930 bound rapidly, reversibly and stereoselectively to a homogeneous population of high affinity recognition sites: $B_{max} = 58 +/ - 3$ fmol/mg protein, $pK_D = 9.01 +/ - 0.08$ ($n = 11$). Non linear regression and Scatchard analysis of saturation data suggested the existence of a single class of [³H]ICS 205-930 recognition sites on NG 108-15 cells. The binding was rapid, stable and reversible. The affinity of [³H]ICS 205-930 determined in kinetic studies was in agreement with that obtained under equilibrium conditions. 3. Competition studies performed with a variety of agonists and antagonists also suggested the presence of a homogeneous population of [³H]ICS 205-930 recognition sites. All competition curves were steep and monophasic and were best fit by a 1 receptor site model. [³H]ICS 205-930 binding sites displayed the pharmacological profile of a 5-HT3 receptor. Potent 5-HT3 receptor antagonists showed nanomolar affinities for [³H]ICS 205-930 binding sites with the following rank order of potency: SDZ 206-830 greater than ICS 205-930 greater than SDZ 206-792 greater than BRL 43694 greater than quipazine greater than BRL 24924 greater than SDZ 210-204 greater than MDL 72222 greater than SDZ 210-205. Metoclopramide, mCP and mianserin showed submicromolar affinity.

- Ondansetron=GR 38032F=SN-307=Zofran®

Ondansetronum INN (Ondansetron)

2,3-Dihydro-9-metyl-3-[(2-metylimidazol-1-yl)metyl]karbazol-4(1H)-on



5 The compound is both an indole derivative and an imidazole. Other imidazole derivatives are listed below.

- GR 38032 F

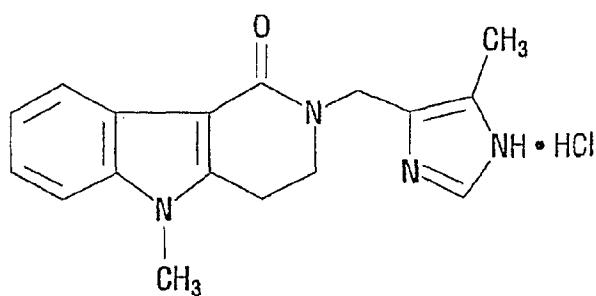
10 Comparison of the 5-HT3 receptor antagonist properties of ICS 205-930, GR38032F and zacopride., Cohen ML, Bloomquist W, Gidda JS, Lacefield W; J Pharmacol Exp Ther 1989 Jan, 248:1:197-201

15 The well-documented 5-HT3 receptor antagonists, ICS 205-930 and GR38032F, have been compared with regard to their inhibitory activity at 5-HT3 receptors to another gastrokinetic agent, zacopride. Zacropride and ICS 205-930 showed similar affinity (-log kB approximately 8.0), whereas GR38032F showed lower affinity (-log ka approximately 7.0) at 5-HT3 receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as 20 inhibitors of serotonin-induced bradycardia (5-HT3-mediated activation of the von Bezold Jarisch

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reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS 205-903, which was approximately 2-fold more potent than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zycopride possessed the longest duration of inhibitory effectiveness in urethane-anesthetized rats with maximal inhibition still apparent 6 hr after oral administration. All three agents inhibited cisplatin-induced emesis after i.v. administration in dogs with zacopride being 10-fold more potent than ICS 205-930 or GR38032F, which were equipotent. These comparative data with three 5-HT3 receptor antagonists indicate that in animals, zacopride was more potent and longer acting than either ICS 205-930 or GR38032F. Furthermore, after oral administration to rats, GR38032F was slightly less potent than ICS 205-930 and possessed the shortest duration of action.

- Alosetron=Lotronex (Glaxo)



The compound is both an indole derivative and an imidazole. Other imidazole derivatives are listed below.

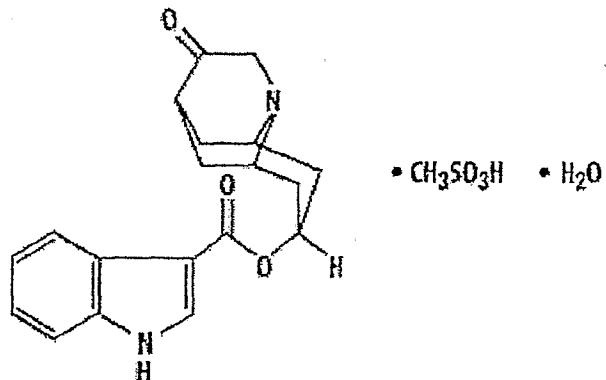
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The pharmacological properties of the novel selective 5-HT3 receptor antagonist, alosetron, and its effects on normal and perturbed small intestinal transit in the fasted rat., Clayton NM, Sargent R, Butler A, Gale J, Maxwell MP, Hunt AA, Barrett VJ, Cambridge D, Bountra C, Humphrey PP; Neurogastroenterol Motil 1999 Jun, 11:3:207-17

The purpose of this study was to investigate the pharmacological properties of the novel, selective 5-HT3 receptor antagonist, alosetron, and its effects on transit time in both the normal and perturbed small intestine of the rat. Alosetron concentration-dependently inhibited radioligand binding in membranes containing rat and human 5-HT3 receptors with estimated pKi values of 9.8 (n = 3) and 9.4 (n = 6), respectively. In selectivity studies alosetron had little or no significant affinity for any of the many other receptors and ion channels studied. Alosetron potently antagonized the depolarization produced by 5-HT in the rat vagus nerve (estimated pKB value of 9.8, n = 25). In anaesthetized rats, i. v. administration of alosetron inhibited 2-methyl-5-HT induced bradycardia (Bezold Jarisch index) at 1 and 3 microg kg-1, with an agonist dose ratio of approximately 3.0 at 1.0 microg kg-1, = 3-5). Alosetron administered via the duodenum also inhibited this reflex, with duration of action that was significantly longer than that seen with ondansetron (120-60 min, respectively, n = 6). Alosetron had no significant effect on normal small intestinal propulsion in the rat, but fully reversed the increase in intestinal propulsion (96%, n = 3)

produced by egg albumin challenge. Alosetron is a highly selective 5-HT3 antagonist which normalizes perturbed small intestinal propulsion. Previous clinical data in IBS patients together with the 5 transit data provide a good rationale for further studies with alosetron in IBS patients.

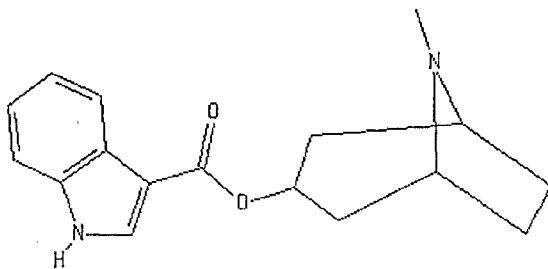
- Bemesetron
- 10 • Galdansetron
- Dolasetron mesilat =MDL73147 EF= Anzemet.
IUPAC name: (2,6,8,9a β)-octahydro-3-oxo-2,6-methano-
2H-quinolizin-8-yl-1H-indole-3-carboxylate
15 monomethanesulfonate, monohydrate.



- Dolasetron=MDL74156
- 20

- Tropisetron =Navoban®

5 IUPAC name: 1aH,5aH - Tropane - 3a - yl-3 - indole-carboxylate



- Zatosetron =LY 277359. The compound is also called LY 19617.

10 The effect of acute and chronic LY 277359, a selective 5-HT3 receptor antagonist, on the number of spontaneously active midbrain dopamine neurons., Minabe Y, Ashby CR Jr, Wang RY; Eur J Pharmacol 1991 Dec 17, 209:3:151-6

15 In this study, we have examined the effect of acute and chronic administration of LY 277359, a putative 5-HT3 receptor antagonist, on the number of spontaneously active dopamine cells in the substantia nigra pars compacta (SNC or A9) and ventral tegmental area (VTA or A10). This was accomplished using the standard extracellular single unit recording techniques. The acute administration of LY 277359 (0.1 or 1.0 mg/kg i.p.) produced a significant increase in the number of spontaneously active A10, but not A9, dopamine cells compared to

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saline controls. The acute administration of 10 mg/kg of LY 277359 did not significantly alter the number of spontaneously active dopamine cells in either area. In contrast to its acute effects, the 5 administration of 0.1 mg/kg per day of LY 277359 for 21 days decreased the number of spontaneously active A9 and A10 dopamine cells. However, the i.v. administration of (+/-)-apomorphine (50 micrograms/kg) did not reverse LY 277359's action, 10 suggesting that the chronic LY 277359-induced reduction of dopamine cells was not the result of depolarization block. To test whether chronic administration of LY 277359 at a high dose would induce depolarization block of dopamine cells, rats 15 were treated with 1.0 or 10 mg/kg LY 277359. Interestingly, the chronic administration of 1.0 mg/kg LY 277359 increased the number of A10, but not A9 dopamine cells. In contrast, chronic treatment with 10 mg/kg selectively decreased the number of 20 spontaneously active A10 dopamine cells.

- GR65630 (3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propanone)
- 25 • GR67330
[3H] GR67330, a very high affinity ligand for 5-HT3 receptors.
Kilpatrick GJ, Butler A, Hagan RM, Jones BJ, Tyers MB Naunyn Schmiedebergs Arch Pharmacol 1990 Jul, 30 342:1:22-30

GR67330 potently inhibited 5-hydroxytryptamine (5-HT)-induced depolarizations of the rat isolated vagus nerve. At the higher concentrations used (0.3 nmol/l-1 nmol/l) this was accompanied by a marked reduction in the maximum response to 5-HT. The 35 calculated pKB value was 10.2. The binding of the

tritiated derivative of GR67330 to homogenates of rat entorhinal cortex was examined. Kinetic analysis revealed that specific [³H] GR67330 (0.1 nmol/l) binding was rapid and reversible. Association and dissociation rate constants were $1.48 +/- 0.36 \times 10(8)$ mol/l⁻¹ s⁻¹ and $7.85 +/- 0.41 \times 10(-3)$ s⁻¹ respectively. Equilibrium saturation analysis revealed specific binding was to a single site (B_{max} $22.6 +/- 0.21$ fmol/mg protein) of high affinity (K_d $0.038 +/- 0.003$ nmol/l). At low ligand concentrations, specific binding was up to 90% of total binding. If unlabelled GR67330 was used to define non-specific binding two sites were evident (K_{d1} $0.066 +/- 0.007$ nmol/l, K_{d2} $20.1 +/- 9.7$ nmol/l; B_{max1} $31.5 +/- 3.2$ fmol/mg protein, B_{max2} $1110 +/- 420$ fmol/mg protein). [³H] GR67330 binding was inhibited potently by 5-HT₃ antagonists and agonists. Ligands for other 5-HT receptors and other neurotransmitter receptors were either only weakly active or inactive at inhibiting binding. Hill numbers for antagonist inhibition of binding were close to unity, except for quipazine which was significantly greater than one. In common with other 5-HT₃ binding studies, all 5-H-agonist tested had Hill numbers greater than one (1.51-1.71). GR38032 and GR65630 inhibited a greater proportion of binding than other 5-HT₃ antagonists, this additional binding was interpreted as inhibition from a second saturable site unrelated to the 5-HT₃ receptor.

- ICS 205-930 ((3 Alpha-Tropanyl)-1H-Indole-3-carboxylic acid ester)
- Comparison of the 5-HT₃ receptor antagonist properties of ICS 205-930, GR38032F and zacopride., Cohen ML, Bloomquist W, Gidda JS, Lacefield W
J Pharmacol Exp Ther 1989 Jan, 248:1:197-201

The well-documented 5-HT3 receptor antagonists, ICS 205-930 and GR38032F, have been compared with regard to their inhibitory activity at 5-HT3 receptors to another gastrokinetic agent, zacopride. Zacopride and ICS 205-930 showed similar affinity (-log kB approximately 8.0), whereas GR38032F showed lower affinity (-log ka approximately 7.0) at 5-HT3 receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as inhibitors of serotonin-induced bradycardia (5-HT3-mediated activation of the von Bezold Jarisch reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS 205-903, which was approximately 2-fold more potent than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zacopride possessed the longest duration of inhibitory effectiveness in urethane-anesthetized rats with maximal inhibition still apparent 6 hr after oral administration. All three agents inhibited cisplatin-induced emesis after i.v. administration in dogs with zacopride being 10-fold more potent than ICS 205-930 or GR38032F, which were equipotent. These comparative data with three 5-HT3 receptor antagonists indicate that in animals, zacopride was more potent and longer acting than either ICS 205-930 or GR38032F. Furthermore, after oral administration to rats, GR38032F was slightly less

potent than ICS 205-930 and possessed the shortest duration of action.

- QICS 205-930

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- 3-Tropanyl-indole-3-carboxylate methiodide. It is also called ICS 205-930.

- Indalpine (3- [2- (4-piperidinyl)ethyl]-1H-indole)

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- VA21B7 (3- [2- (4'-piperonylpiperazinyl) indolyl] carboxaldehyde)

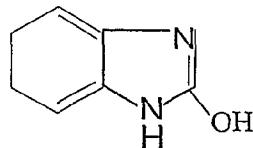
15 The pharmacology of VA21B7: an atypical 5-HT3 receptor antagonist with anxiolytic-like properties in animal models. Artaiz I, Romero G, Zazpe A, Monge A, Calderó JM, Roca J, Lasheras B, Del Río J
Psychopharmacology (Berl) 1995 Jan, 117:2:137-48

20 VA21B7 (3- [2- (4'-piperonylpiperazinyl) indolyl] carboxaldehyde) was synthesized as a potential 5-HT3 receptor antagonist. Even though VA21B7 showed a higher affinity towards 5-HT3 receptors as compared to other receptors studied, it was not a potent 25 5-HT3 receptor antagonist either in the periphery or in the brain. In a simple animal model of anxiety such as the two-compartment box in mice, a remarkable anxiolytic-like effect was found at doses of 2-500 micrograms/kg IP and also at low oral 30 doses, in the microgram range. These drug doses did not produce any significant effect on spontaneous motor activity of mice. The anxiolytic profile of VA21B7 was further explored using other models of anxiety in rats such as the elevated plus-maze and 35 punished-drinking. VA21B7 was compared with standard 5-HT3 receptor antagonists such as ondansetron, tropisetron and granisetron, with the 5-HT1A agent

buspirone and with diazepam. In the plus-maze, VA21B7 showed an anxiolytic-like profile after doses of 0.25-0.5 mg/kg IP or 2-4 mg/kg PO which did not modify the number of total entries into the open and closed arms of the maze. Diazepam, granisetron and tropisetron were also effective in this test but not ondansetron and buspirone. VA21B7 was also able to release suppressed behaviour in the punished-drinking test. The dose-response curve was bell-shaped with a peak at 2-4 mg/kg. At variance with other studies, 5-HT3 receptor antagonists also increased the number of shocks taken in this test and the dose-response curve was also bell-shaped. VA21B7 was not anticonvulsant like diazepam, its anxiolytic action in the light/dark test was not flumazenil-sensitive and there was no rebound anxiogenic effect on withdrawal from chronic VA21B7 treatment for 15 consecutive days. Moreover, VA21B7 was not amnesic like the benzodiazepines but low doses of 2-4 mg/kg reduced the memory deficits induced in rats by scopolamine. Much higher doses were necessary to decrease spontaneous motor activity in rats. Since VA21B7 appears to be well tolerated in rodents at high doses, we think that it is of potential interest as an anxiolytic in humans.

Benzimidazolones, benzimidazoles and other imidazoles

The common chemical structure of a benzimidazolone is:



- Iodophenpropit (4-(1H-imidazol-4-yl-methyl)-piperidine)

- BIMU 1 (endo-N- (8-methyl-8-azabicyclo[3.2.1.]oct-3-yl)- 2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride)

5

- 2-piperazin-benzimidazole
- 2-piperidin-benzimidazole

10

- Cilansetron (1-10- [(2-methyl-1H-imidazol-1-yl)methyl]-5,6,8,9,10,11-hexahydro-4H-pyrido [3,2,1-jk] carbazol-11-one hydrochloride)

15

- GK 128 (2- [(2-methylimidazol-1-yl)methyl]benzo[i]-thiochromen-1-one monohydrochloride hemihydrate
Effect of a novel 5-hydroxytryptamine3 (5-HT3) receptor antagonist, GK-128, on 5-HT3 receptors mediating contractions and relaxations in guinea-pig distal colon.

20

Ito C, Kawamura R, Isobe Y, Tsuchida K, Muramatsu M, Higuchi S;

Gen Pharmacol 1997 Sep, 29:3:353-9

25

We investigated 5-hydroxytryptamine3 (5-HT3) receptor-mediating contractions and relaxations in the guinea-pig isolated distal colon using various 5-HT3 receptor agonists and antagonists, including GK-128 (2- [(2-methylimidazol-1-yl) methyl] benzo[f] thiochromen-1-one monohydrochloride hemihydrate).

30

2. Selective 5-HT3 receptor agonists, 2-methyl-5-HT and m-chlorophenylbiguanide, produced spantide-insensitive contraction and atropine-insensitive contraction and the relaxation. These agonists showed a small, but significant, difference of potency between contraction and relaxation. 3. GK-128 competitively blocked both 2-methyl-5-HT- and m-chlorophenylbiguanide-induced responses with similar

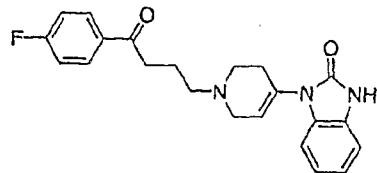
35

potency. The affinities of GK-128 for spantide-insensitive contraction and atropine-insensitive contraction were ten-fold higher than for relaxation. 4. Other selective 5-HT3 receptor antagonists, azasetron and tropisetron, also exhibited higher affinity in contraction than in relaxation, but the extent of their affinity differences was smaller than that observed in GK-128. In contrast, granisetron, ramosetron and ondansetron exhibited no significant differences in their affinity values among the three responses. 5. These results suggest that the 5-HT3 receptors which mediate contraction and relaxation in the guinea-pig distal colon may not be the same, and that GK-128 is a 5-HT3 receptor antagonist with a stronger potency for contraction.

- Droperidol. Ingår i Dridol, Janssen-Cilag

Droperidolum INN (Droperidol)

1-[1-(3-(4-Fluorobensoyl)propyl)-1,2,3,6-tetrahydro-4-pyridyl]-1,3-dihydro-2H-benzimidazol-2-on



20 • KAE-393/YM-114
 ((R)-5-[(2,3-dihydro-1-indolyl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole

25 Comparison of the effects of trimebutine and YM114 (KAE-393), a novel 5-HT3 receptor antagonist, on

stress-induced defecation. Miyata K, Ito H, Yamano M, Hidaka K, Kamato T, Nishida A, Yuki H; Eur J Pharmacol 1993 Dec 7, 250:2:303-10

5 YM114 (KAE-393), (R)-5-[(2,3-dihydro-1-indolyl)- carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole hydrochloride, is a derivative of YM060, a potent 5-HT3 receptor antagonist. We investigated the effects 10 of YM114 on 5-HT3 receptors, both in vitro and in vivo, and on bowel dysfunction induced by restraint stress, 5-HT and thyrotropin-releasing hormone (TRH), and compared them with the effect of trimebutine. YM114 dose dependently inhibited the reduction in heart rate induced by 5-HT (30 15 micrograms/kg i.v.) in rats (ED50 = 0.31 micrograms/kg i.v.), and the potency of YM114 was almost the same as that of the racemate. The S-form of YM114 also inhibited 5-HT-induced bradycardia, but 1350 times less potent than the R-form. YM114 20 and its S-form inhibited [³H]GR65630 binding to NIE-115 cell membranes in a concentration-dependent manner with Ki values of 0.341 and 616 nM, respectively, showing the isomeric activity ratio (R-/S-form) of YM114 to be much greater (1800). 25 YM114 antagonized 5-HT-induced depolarization of the nodose ganglion (EC50 = 1.39 nM). Trimebutine (1 mg/kg i.v.) failed to inhibit 5-HT-induced bradycardia, implying that it does not possess 5-HT3 receptor antagonistic activity. YM114 significantly 30 and dose dependently prevented restraint stress-, 5-HT- and TRH-induced increases in fecal pellet output, and restraint stress- and 5-HT-induced diarrhea in rats and mice (ED50 = 6.9, 72.5, 154.6, 9.7 and 52.4 micrograms/kg p.o., respectively). 35 Trimebutine significantly prevented stress- and 5-HT-induced diarrhea (ED50 = 29.4 and 87.3 mg/kg p.o., respectively), but only partially affected

stress-, 5-HT- and TRH-induced increases in fecal pellet output. Thus, YM114 is a potent and stereoselective 5-HT3 receptor antagonist with much greater protective effects against stress-induced defecation than trimebutine.hydrochloride).

5

- Itasetron=DAU6215 ((3-alpha-tropanyl)1H-benzimidazolone-3-carboxamide chloride) Intravenous itasetron: establishing the effective dose range for the prophylactic control of acute emesis in cancer patients undergoing high-dose cisplatin chemotherapy., Patoia L, Del Favero A, Giglietti A, Malacarne P, Donati D, Indelli M, Bensi G, Palladino MA, Cigarini P, Kempe R, Voigt T; Clin Oncol (R Coll Radiol) 1999, 11:2:99-104

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15

Nausea and vomiting induced by chemotherapy are a major cause of distress to patients and reduce compliance with potentially beneficial treatment.

20 Itasetron hydrochloride is a new 5-hydroxytryptamine3 (5-HT3) antagonist with potent antiemetic properties. It is more potent than ondansetron in animal models and in early clinical studies it demonstrates a long half-life and does not undergo hepatic biotransformation before elimination. The aim of this open, uncontrolled study was to establish the effective dose range of itasetron hydrochloride given intravenously (i.v.) to patients due to receive high-dose cisplatin chemotherapy (50-120 mg/m²) for the first time.

25

30 Thirty-nine patients were enrolled in the trial and received a single i.v. infusion of itasetron hydrochloride at a dose of 17-280 microg/kg body weight before commencing the cisplatin infusion (median dose 90-110 mg/m²). Antiemetic protection was demonstrated by doses in the range of 35-280 microg/kg. The 17 microg/kg dose was not effective.

35

Treatment failure (>5 emetic episodes/24 hours) was reported in only six (16%) of the 38 evaluable patients over all treatment groups. Adverse events were generally mild or moderate and of a similar type and incidence to those of current 5-HT3 antagonists. Physicians' and patients' assessments of efficacy and tolerability of itasetron hydrochloride were similar, the majority rating the treatment as 'good' or 'very good'. In conclusion, itasetron hydrochloride is effective in the dose range 35-280 microg/kg in preventing cisplatin-induced emesis. Taken together with results from a larger dose-finding study, a dose corresponding to 35 microg/kg (equivalent to 2.5 mg itasetron, calculated as free base) has been pursued in Phase III studies with the i.v. formulation.

- Lerisetron

20 New 2-piperazinylbenzimidazole derivatives as 5-HT3 antagonists. Synthesis and pharmacological evaluation. Orjales A, Mosquera R, Labeaga L, Rodes R
J Med Chem 1997 Feb 14, 40:4:586-93

25 A series of 2-piperazinylbenzimidazole derivatives were prepared and evaluated as 5-HT3 receptor antagonists. Their 5-HT3 receptor affinities were evaluated by radioligand binding assays, and their abilities to inhibit the 5-HT-induced Bezold-Jarisch reflex in anesthetized rats were determined. Compound 7e (lerisetron, $pKi = 9.2$) exhibited higher affinity for the 5-HT3 receptor than did tropisetron and granisetron, while compound 7q ($pKi = 7.5$) had very low affinity for this receptor, showing that substitution on the N1 atom of the benzimidazole ring is essential for affinity and activity. The

effect of substitution on the aromatic ring of benzimidazole by several substituents in different positions is also discussed. A strong correlation between the 5-HT3 antagonistic activity of the studied compounds and the position of substitution on the aromatic ring was established. Thus, while the 4-methoxy derivative 7m showed weak affinity for the 5-HT3 receptor ($pKi = 6.7$), the 7-methoxy derivative 7n exhibited the highest affinity ($pKi = 9.4$). Compounds 7e and 7n are now under further investigation as drugs for the treatment of nausea and emesis evoked by cancer chemotherapy and radiation.

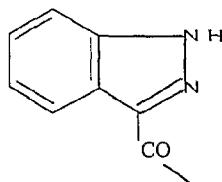
15 • Eurosetron

20 • Mirisetron =WAY100579

25 • Ramosetron =YM 060. [(R)-5-[(1-methyl-3-indolyl)- carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole hydrochloride]

Indazole carboxamide derivatives

25 The compounds have the general structure.



30 • AS5370 ((+/-)-N-[1-methyl-4-(3-methyl-benzyl)- hexahydro-1H-1,4-diazepin-6-yl]-1H-indazole-3-carboxamide dihydrochloride). The compound is also a diazepin derivative.

- DAT582 (the compound is the R- enantiomer of compound AS5370) 5-HT3 receptor antagonist effects of DAT-582, (R) enantiomer of AS-5370.

5 Yoshida N, Omoya H, Kato S, Ito T, Eur J Pharmacol
1992 Jun 17, 216:3:435-40

The serotonin 5-HT3 receptor antagonist effects of DAT-582, the (R) enantiomer of AS-5370 ((+/-)-N-[1-methyl-4-(3-methyl-benzyl)hexahydro-1H-1,4-diazepin-6-yl]-1H-indazole-3-carboxamide dihydrochloride), and its antipode were compared with those of AS-5370 and existing 5-HT3 receptor antagonists. In anesthetized rats, DAT-582 antagonized 2-methyl-5-HT-induced bradycardia with an ED50 value of 0.25 microgram/kg i.v., whereas the (S) enantiomer was without effect even at 1000 micrograms/kg i.v. In antagonizing the bradycardia, DAT-582 was as potent as granisetron, slightly more potent than AS-5370, and 2, 5 and 18 times more potent than ondansetron, ICS 205-903 and renzapride, respectively, although it was less potent than zacopride. DAT-582 inhibited cisplatin (10 mg/kg i.v.)-induced emesis in ferrets with an ED50 value of 3.2 micrograms/kg i.v. twice. The antiemetic activity of DAT-582 was more potent than that of the existing 5-HT3 receptor antagonists examined, except zacopride. In contrast, the (S) enantiomer had little effect at 1000 micrograms/kg i.v. twice. In isolated guinea-pig ileum, DAT-582 inhibited 5-HT-induced contractions with an IC50 value of 91 nM, whereas the (S) enantiomer hardly inhibited them even at 1000 nM. These results suggest that DAT-582, the (R) enantiomer of AS-5370, potently and selectively blocks 5-HT3 receptors.

35 • N-3389 (N-3389 (endo-3,9-dimethyl-3,9-diazabicyclo[3.3.1]non-7-yl 1H-indazole-3-carboxamide dihydrochloride)

5 Antagonistic activities of N-3389, a newly synthesized diazabicyclo derivative, at 5-HT3 and 5-HT4 receptors., Hagiwara K, Hayakawa T, Arai T, Eguchi H, Mino S, Kawase S, Eur J Pharmacol 1994 Dec 12, 271:1:159-66

10 The antagonistic activities of compound N-3389 (endo-3,9-dimethyl-3,9-diazabicyclo[3.3.1]non-7-yl 1H-indazole-3-carboxamide dihydrochloride) at 5-HT3 and 5-HT4 receptors were examined using in vitro and in vivo assays. N-3389 showed potent 5-HT3 receptor antagonistic activities in a radioligand binding assay ($pK_i = 8.77$), against 2-methyl-5-HT (2-Me-5-HT)-induced bradycardia in rats ($ED_{50} = 0.73$ micrograms/kg i.v., 38 micrograms/kg p.o.) and against 2-Me-5-HT-induced contraction in longitudinal muscle myenteric plexus preparations of guinea-pig ileum ($IC_{50} = 3.2 \times 10(-8)$ M). As a preliminary to investigating the effect of N-3389 on 5-HT4 receptors, we examined the contraction induced by 5-HT in guinea-pig ileum preparations. We confirmed that 5-HT ($10(-8)$ - $10(-5)$ M) induced biphasic contractions in the preparations.

15 20 Furthermore, 5-HT3 receptor antagonism inhibited the late phase of the contraction induced by high concentrations of 5-HT ($3 \times 10(-6)$ - $10(-5)$ M), whereas 5-HT4 receptor antagonism inhibited the early phase of the contraction induced by low concentrations of 5-HT ($10(-8)$ - $10(-6)$ M). N-3389 ($10(-7)$ - $10(-5)$ M) inhibited both phases of contraction induced by 5-HT. In addition, N-3389 ($3 \times 10(-7)$ - $3 \times 10(-6)$ M) was found to inhibit the increase of electrically stimulated twitch responses induced by 5-HT ($10(-8)$ M) longitudinal muscle myenteric plexus preparation of the guinea-pig ileum. These results

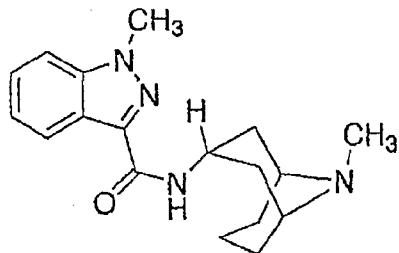
25 30 35

suggest that N-3389 acts as a 5-HT3 and 5-HT4 receptor antagonist.

- BRL 43694=Kytril® =Granisetron

Granisetronum INN (Granisetron)

1-Metyl-N-(*endo*-9-metyl-9-azabicyklo[3.3.1]non-3-yl)-1*H*-indazol-3-karboxamid



5

Selective and functional 5-hydroxytryptamine3 receptor antagonism by BRL 43694 (granisetron).; Sanger GJ, Nelson DR Eur J Pharmacol 1989 Jan 10, 159:2:113-24

10

The activity of BRL 43694 (granisetron) was investigated using established models of 5-HT3 receptor activity. In guinea-pig isolated ileum, BRL 43694 antagonised the contractions evoked by relatively high concentrations of 5-HT ($pA_2 = 8.1 \pm 0.2$). However, except in high concentrations, BRL 43694 did not affect the contractions of similar preparations of ileum, evoked by electrical field stimulation (cholinergically mediated), the nicotinic agonist dimethylphenyl piperazinium (DMPP) or by cholecystokinin octapeptide. Similarly, BRL 43694 did not affect electrically evoked, cholinergically mediated contractions of rat or human isolated stomach. In other models of 5-HT3 receptor activity (rabbit isolated heart, Bezold-Jarisch reflex in anaesthetised rats), potent antagonism by BRL 43694 was demonstrated. In

15

20

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radioligand binding studies on rat brain membranes, BRL 43694 had little or no affinity for 5-HT1A, 5-HT1B, 5-HT2 or for many other binding sites. BRL 43694 may therefore be a potent and selective 5-HT3 receptor antagonist.

5

- Litoxetine=SL81.0385

10 Litoxetine: a selective 5-HT uptake inhibitor with concomitant 5-HT3 receptor antagonist and antiemetic properties. Angel I, Schoemaker H, Prouteau M, Garreau M, Langer SZ.; Eur J Pharmacol 1993 Mar 2, 232:2-3:139-45

15 The selective 5HT uptake inhibitor, litoxetine (SL 81.0385), currently under development as an antidepressant was shown to have antiemetic properties in the ferret. Litoxetine (at 1 and 10 mg/kg i.v.) dose dependently reduced the number of 20 retches and vomiting as well as the number of emetic episodes induced by cisplatin (10 mg/kg i.v.) and delayed the onset of emesis. Fluoxetine (at 1 or 10 mg/kg i.v.) failed to inhibit cisplatin-induced 25 emetic responses and, in contrast, significantly increased the number of retches and vomiting and accelerated the onset of emesis. The possibility that the antiemetic effects of litoxetine may be mediated through an interaction with 5HT3 receptors 30 was studied using [³H]quipazine or [³H]BRL 43694 to label the 5HT3 receptor. Litoxetine has moderate affinity for cerebral 5HT3 receptors (Ki = 85 nM), while fluoxetine, similar to other 5HT uptake 35 inhibitors, has only negligible affinity for this receptor (Ki = 6.5 microM). It is proposed that litoxetine inhibits cisplatin-induced emetic responses due to its moderate 5HT3 antagonist properties. The clinical use of the majority of

serotonergic antidepressants (e.g. fluoxetine, fluvoxamine etc.) is associated with 5
gastrointestinal discomfort (particularly nausea and
vomiting) as a major side-effect. If nausea and
vomiting associated with the use of 5 HT uptake
inhibitors are due to stimulation of 5HT3 receptors,
the concomitant 5HT3 antagonism of litoxetine may
limit the gastrointestinal side-effects of this
novel antidepressant and thus offer an important
10 advantage.

- LY 278584 ((1-methyl-N-(8-methyl-8-azabicyclo-[3.2.1.]oct-3-yl)-1H-indazole-3-carboxamide)

15 Specific [³H]LY278584 binding to 5-HT3 recognition sites in rat cerebral cortex.

Wong DT, Robertson DW, Reid LR; Eur J Pharmacol 1989 Jul 4, 166:1:107-10

20 Binding of [³H]LY278584 a 1-methyl-indazole-carbox-
amide, to putative 5-HT3 recognition sites in mem-
branes isolated from cerebral cortex of rat brain,
is examined. Specific binding of [³H]LY278584
accounts for 83-93% of total binding. The unlabelled
25 LY278584 has 500 times greater affinity for
[³H]LY278584 recognition sites than its 2-methyl
analogue (LY278989), and their potencies parallel
their antagonism of the peripheral 5-HT3 receptors.
Moreover, the order of potencies of other known
30 antagonists of 5-HT3 receptors supports the
conclusion that [³H]LY278584 binds to putative 5-HT3
receptors in cortical membranes.

- LY-278,584 maleate, see above.
- LY258-458

• LY 278989

Specific [³H]LY278584 binding to 5-HT₃ recognition sites in rat cerebral cortex.

Wong DT, Robertson DW, Reid LR; Eur J Pharmacol 1989 Jul 4, 166:1:107-10

Binding of [³H]LY278584 a 1-methyl-indazole-carboxamide, to putative 5-HT₃ recognition sites in membranes isolated from cerebral cortex of rat brain, is examined. Specific binding of [³H]LY278584 accounts for 83-93% of total binding. The unlabelled LY278584 has 500 times greater affinity for [³H]LY278584 recognition sites than its 2-methyl analogue (LY278989), and their potencies parallel their antagonism of the peripheral 5-HT₃ receptors. Moreover, the order of potencies of other known antagonists of 5-HT₃ receptors supports the conclusion that [³H]LY278584 binds to putative 5-HT₃ receptors in cortical membranes.

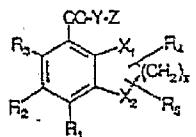
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• LY-211-000

Benzofuranes, benzooxazines, benzo(di)azepines, bensothiazepines

25

A general structure for these classes of compounds is:

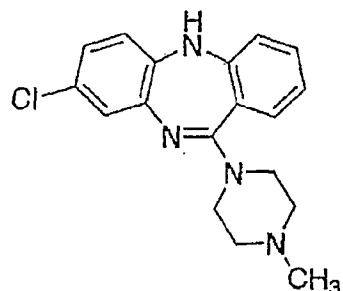


- 2,3-dihydro-benzofuran-7-carboxamides. X1=C, X2=O; five-membered ring system.
- 5 • RG 12915 ([4-[N-(1-azabicyclo[2.2.2.]octan-3-(S)-yl)]2-chloro-cis 5a-(S)-9a-(S)-5a,6,7,8,9,9a-hexahydrobenzofurancarboxamide hydrochloride])
- 10 • ADR 851 [4-amino-5-chloro-2,3-dihydro-N-(pyrrolidin-2-ylmethyl)benzofuran-7-carboxamide
- ADR-882
Analgesic effects of S and R isomers of the novel 5-HT3 receptor antagonists ADR-851 and ADR-882 in rats.; Sufka KJ, Giordano J, Eur J Pharmacol 1991 Oct 29, 204:1:117-9

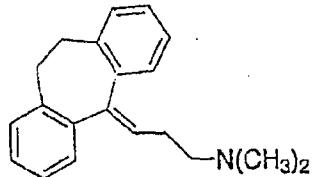
15 The present study examined analgesia produced by S and R isomers of the novel 5-HT3 receptor antagonists, ADR-851 and ADR-882 (0.1-10 mg/kg s.c.) against acute thermal, mechanical and formalin-induced inflammatory pain in rats. Neither isomer of ADR-851 or ADR-882 was analgesic in the thermal or mechanical test. Similarly, neither S or R forms of ADR-882 produced significant anti-nociception in the formalin test. In contrast, ADR-851R produced significant analgesia at 3 and 10 mg/kg doses in this test, while ADR-851S produced significant analgesia only at 1 mg/kg.

20

- RP 62203 (2-[3-(4-(4-fluorophenyl)-piperazinyl)-propyl]naphto[1,8-*ca*]isothiazole-1,1-dioxide)
- 25 • Clozapine. Ingår i Leponex, Novartis

Clozapinum INN (Klozapin)8-Kloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b,e*][1,4]diazepin

- Amitriptyline

Amitriptylinum INN (Amitriptylin)5-(3-Dimethylaminopropyliden)-10,11-dihydro-5*H*-dibenz[*a,d*]cyklohepten

5

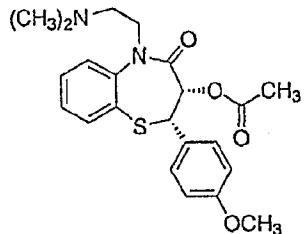
- Cyproheptadine. Is the active ingredient of
Periactin, MSD
- Diltiazem

69

Is the active ingredient in Cardizem, Pharmacia
Corporation

Diltiazemum INN (Diltiazem)

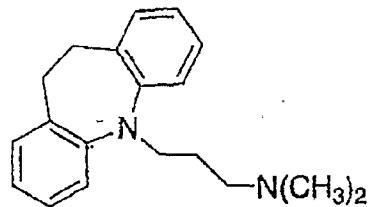
(2*S*,3*S*)-3-(Acetoxy)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one



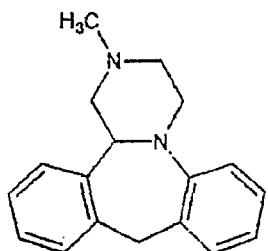
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- Imipramin

5-(3-Dimethylaminopropyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin



- Mianserin



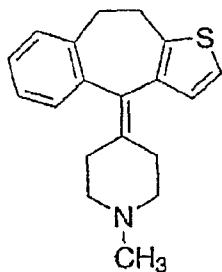
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70

- Mirtazapine (1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a] pyrido [2,3-c] benzazepine)
- Pizotifen

Pizotifenum INN (Pizotifen)

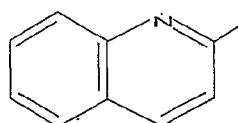
4-(1-Methyl-4-piperidyliden)-9,10-dihydro-4H-benzo-[4,5]cyklohepta[1,2-b]tiofen



5

Quinolines, quinolizines and isoquinolines

10 The common structure of quinoline is:



Isoquinoline and quinolizine are isomers of quinoline.

15

- Quinoline-3-carboxamides
- Quinoline-4-carboxylates
- Isoquinoline-1-one (isomer till quinolin-1-one)

20

- SEC 579
- RS 56532 ((S)-6-amino-5-chloro-2-(1-azabicyclo-[2, 2, 2]octan-3-yl) 2,3-dihydro-1H-benz[de] -

isoquinoline-1,3-dione hydrochloride)

- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile
- 5 • 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile
- KF 17643 (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl-2-(n-propyloxy)-4-quinolinecarboxylate)
- 10 • KF 18259 ((endo-(8-methyl-8-aza- bicyclo[3.2.1]oct-3-yl)-1-isobutyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride)
- 15 • KF 20170 (endo-N-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-4-hydroxy-3- quinolinecarboxamide

- Palonosetron=RS 25259-197
20 (S)-2- [(S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]-isoquinoline-hydrochloride
- Quipazine (2-(1-piperazinyl)-Quinoline)
- 25 • N-methylquipazin
- 4-Ph-N-Me-quipazine
- 30 • RS-42358-197 [(S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1 H-benzo[de]isoquinolin-1-one hydrochloride]
- 35 • RS-056812-198 (R)-N-(quinuclidin-3-yl)-2-(1-methyl-1 H-indol-3-yl)-2-oxo-acetamide

- RS-25259-197 [(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]- isoquinoline-hydrochloride)

5 The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT3 receptors, in vitro. Wong EH, Clark R, Leung E, Loury D, Bonhaus DW, Jakeman L, Parnes H, Whiting RL, Eglen RM, Br J Pharmacol 1995 Feb, 114:4:851-9

10 A series of isoquinolines have been identified as 5-HT3 receptor antagonists. One of these, RS 25259-197 [(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzc[de]iso-15 quinoline-hydrochloride], has two chiral centres. The remaining three enantiomers are denoted as RS 25259-198 (R,R), RS 25233-197 (S,R) and RS 25233-198 (R,S). 2. At 5-HT3 receptors mediating contraction of guinea-pig isolated ileum, RS 25259-20 197 antagonized contractile responses to 5-HT in an unsurmountable fashion and the apparent affinity (pKB), estimated at 10 nM, was 8.8 +/- 0.2. In this tissue, the -log KB values for the other three enantiomers were 6.7 +/- 0.3 (R,R), 6.7 +/- 0.1 (S,R) and 7.4 +/- 0.1 (R,S), respectively. The apparent affinities of RS 25259-197 and RS 25259-25 198, RS 25233-197 and RS 25233-198 at 5-HT3 receptors in membranes from NG-108-15 cells were evaluated by a [³H]-quipazine binding assay. The -log Ki values were 10.5 +/- 0.2, 8.4 +/- 0.1, 8.6 +/- 0.1 and 9.5 +/- 0.1, respectively, with Hill coefficients not significantly different from unity. Thus, at these 5-HT3 receptors, the rank order of apparent affinities was (S,S) > (R,S) > (S,R) = (R;R). 3. RS 25259-197 displaced the binding of the selective 5-HT3 receptor ligand, [³H]-RS 42358-197, in membranes from NG-108-15 cells, rat cerebral

cortex, rabbit ileal myenteric plexus and guinea-pig ileal myenteric plexus, with affinity (pKi) values of 10.1 +/- 0.1, 10.2 +/- 0.1, 10.1 +/- 0.1 and 8.3 +/- 0.2, respectively.

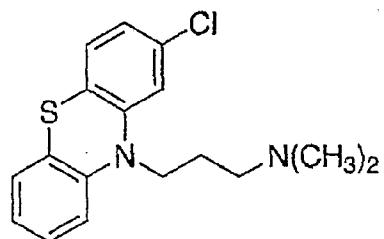
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Phenthiazines and Benzoxazines

- Chlorpromazine

Chlorpromazinum INN (Klorpromazin)

10-(3-Dimethylaminopropyl)-2-klorofentiazin

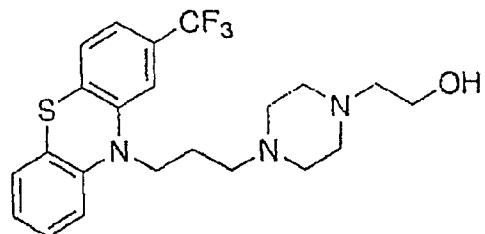


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- Cyamemazine (10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile)
- Fluphenazin

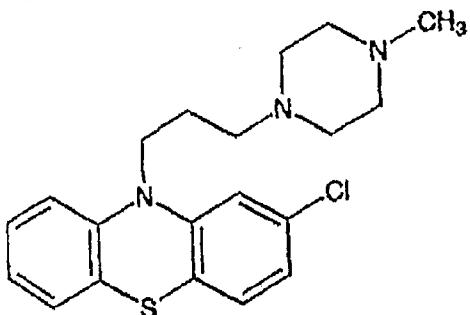
Fluphenazinum INN (Flufenazin)

10-[3-(4-(2-Hydroxyethyl)-1-piperazinyl)propyl]-2-trifluoromethylfentiazin



15

- Prochlorperazine=Stemetil

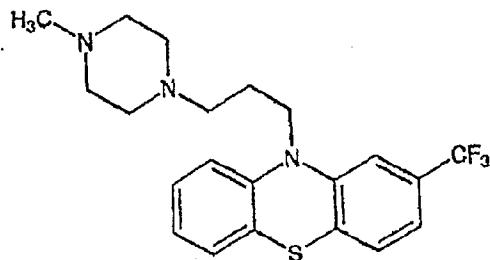


- KB-6933 (6-amino-5-chloro-1-isopropyl-2-(4-methyl-1-piperazinyl)benzimidazole dimaleate)

5

- Perfenazine. Ingår i Trilafon. Cl istället för CF₃ i formeln för Flufenazine
- Trifluoperazine

10



- Azasetron=Y25130 (+/-)-N-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide monohydrochloride

15

Pharmacokinetics of azasetron (Serotone), a selective 5-HT₃ receptor antagonist.

Tsukagoshi S Gan To Kagaku Ryoho 1999 Jun, 26:7:1001-8

20

5-HT₃ receptor antagonists have been established in a number of clinical trials as effective agents in the management of nausea and vomiting induced by

cancer chemotherapy including cisplatin. Azasetron (Serotone) is a potent and selective 5-HT3 receptor antagonist, and classified as benzamide derivative. It has a different chemical structure from indole-type 5-HT3 receptor antagonists such as granisetron, ondansetron, ramosetron and tropisetron. The major difference is found in the pharmacokinetic profiles. Approximately 60-70% of azasetron administered i.v. and orally is excreted in urine as the unmetabolized form. Also, orally-administered azasetron has shown to be absorbed and/or secreted by the saturable transport mechanism in the small intestine, resulting in good bioavailability as approximately 90%. In this report, the relationship between the structure of 5-HT3 receptor antagonists (especially azasetron) and their pharmacokinetics were described.

- 5-((Dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole
- 1,4-Benzoxazin-8-Carboxamide

25

Other compounds, including piperidines, piperazines, alkaloides, benzoates and ureas

- Anpirtoline (6-Chloro-2-[piperidinyl-4-thio]-pyridine)
- Ritanserin
- NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-butyl] piperazine)
- Naphtimides.
- TFMPP (1-(3-trifluoromethylphenyl)piperazine)

- Ifenprodil (dl-erythro-4-benzyl-alpha-(4-hydroxy-phenyl)-beta-methyl-1-piperidine-ethanol tartrate) (ifenprodil tartrate)

5 • MCPP (Meta-chlorophenylpiperazine) (mCPP)

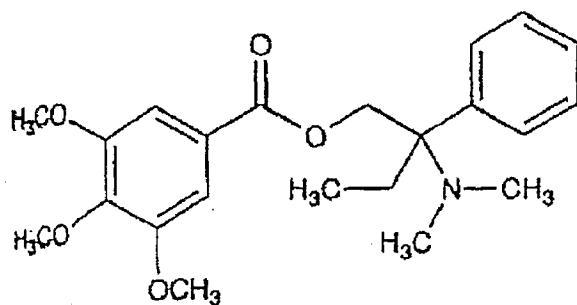
- MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine)

10 • Metergoline ([(8{BETA})-1,6-dimethylergolin-8-yl]methyl]-Carbamic acid phenylmethyl ester)

- Methysergide (1-methyl-D-lysergic acid butanolamide)
- S-apomorfin

15 • Tropanyl-3,5-dimethylbenzoate

- Trimebutine, ett 3,4,5-trimetoxybenzoate derivat.



20 • TMB-8 (8-(N,N-diethylamino)octyl 3,4,5-trimethoxybenzoate)

- Phenylbiguanide

25 Functional characterization of a 5-HT3 receptor which modulates the release of 5-HT in the guinea-pig brain., Blier P, Bouchard C Br J Pharmacol 1993 Jan, 108:1:13-22

The aims of the present study were to confirm the modulation by 5-HT3 receptors of the electrically evoked release of tritium from slices preloaded with [3H]-5-HT of guinea-pig frontal cortex, hippocampus and hypothalamus, and to assess their functional role in 5-HT release. 2. The selective 5-HT3 agonist, 2-methyl-5-HT, introduced 8 min before the electrical stimulation, enhanced in a concentration-dependent manner the evoked release of [3H]-5-HT in the three brain regions studied. The 5-HT3 agonists, phenylbiguanide and m-chlorophenyl-biguanide, did not enhance the release of tritium in frontal cortex and hypothalamus slices. 3. In hypothalamus slices, this response was lost when 2-methyl-5-HT was introduced 20 min before the stimulation, thus indicating that these 5-HT3 receptors desensitize rapidly. When 2-methyl-5-HT was added 20-min before the first stimulation period to desensitize the 5-HT3 receptors, removed for 24 min, and then re-introduced 8 min before the second stimulation period, the enhancing effect of 2-methyl-5-HT was restored, thus indicating that these 5-HT3 receptors can rapidly regain normal sensitivity. 4. The enhancing effect of 2-methyl-5-HT was attenuated by the 5-HT3 receptor antagonists m-chlorophenylpiperazine = quipazine = ondansetron > or = ICS 205-930 = BRL 24924 > MDL 72222 = zacopride. 5. The 5-HT reuptake blocker, paroxetine, enhanced the electrically evoked release of tritium when introduced 8 min before stimulation; this effect of paroxetine was blocked by ICS 205-930, thus indicating that these 5-HT3 receptors can be activated by endogenous 5-HT. 6. In the absence of electrical stimulation, 2-methyl-5-HT (10 microM) produced a marked enhancement of the basal release of [3H]-5-HT which was calcium-dependent and blocked by S-zacopride but not by paroxetine. 7. The

enhancing effect of 2-methyl-5-HT was dependent both on the frequency of stimulation, as indicated by the attenuated effect of 120 stimulations delivered at 1 Hz instead of 5 Hz, and on the duration of the stimulation, as indicated by the more pronounced effect of pulses delivered at 5 Hz for 24 s instead of 72 s or 120 s. McNeil-A-343 (4-(m-chlorophenyl-carbamoyloxy)-2-butynyl-trimethylammonium chloride).

10 • MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3'-yl-3,5-dichlorobenzoate)

15 MDL 72222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors., Fozard JR Naunyn Schmiedebergs Arch Pharmacol 1984 May, 326:1:36-44

20 The properties of MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3'-yl-3,5-dichlorobenzoate), a novel compound with potent and selective blocking actions at certain excitatory 5-hydroxytryptamine (5-HT) receptors on mammalian peripheral neurones, are described. On the rabbit isolated heart, MDL 72222 was a potent antagonist of responses mediated through the receptors for 5-HT present on the terminal sympathetic fibres. The threshold for antagonism was approximately 0.1 nM and the negative logarithm of the molar concentration of MDL 72222 which reduced the chronotropic response of the isolated rabbit heart to twice an ED₅₀ of 5-HT to that of the ED₅₀ was 9.27. MDL 72222 was also highly selective since responses to the nicotine receptor agonist, dimethylphenylpiperazinium iodine (DMPP), were inhibited only at concentrations more than 1000 times those necessary to inhibit 5-HT. In the anaesthetized rat, MDL 72222 produced marked blockade of the Bezold-Jarisch effect of 5-HT.

Again, inhibition was selective since much higher doses of MDL 72222 failed to alter the response to electrical stimulation of the efferent vagus nerves.

In contrast, MDL 72222 proved only a weak and 5 essentially non-selective antagonist of responses mediated by the 5-HT M-receptor present on the cholinergic nerves of the guinea-pig ileum. MDL 72222 does not block smooth muscle contractile 10 responses elicited by oxytocin or mediated through 5-HT D-receptors, muscarinic or nicotinic cholinoreceptors or histamine H1-receptors except at relatively high concentrations.

- MDL 72699 MDL 72699 är kvartenära saltet av MDL 15 72222.

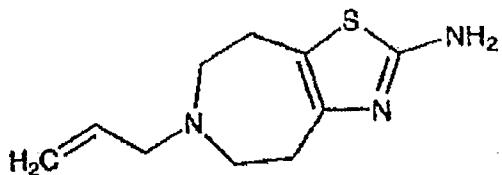
- Mepyramine (N,N-dimethyl N'-(methoxy-4 benzyl)-N'-(pyridyl-2)ethylenediamine) .

- Galanolactone= Gingerol

The irregularly shaped roots (rhizomes) of ginger (*zingiber officinale*) are used extensively in Chinese, Indian, and Japanese cultures where they are believed to have anti-inflammatory, analgesic, 25 cholesterol-lowering, and antithrombotic properties.

Although ginger has been evaluated for the treatment of nausea and vomiting associated with hyperemesis gravidarum, anesthesia, and chemotherapy, this review will focus on ginger for motion sickness.

- Talipexole



Additional compounds

5 • YM 26103-2
• YM 26308-2
• M-840 ([[3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5-yl]-methyl]trimethyl-ammonium iodide)

10 Ref. A mechanism of 5-HT3 receptor mediation is involved etiologically in the psychological stress lesion the stomach of the mouse. , J Pharmacol Exp Ther, 1994 Oct, 271:1, 100-6

15 The role of brain amines, possibly involved in psychological stress, was evaluated and we postulate that the 5-hydroxytryptamine 5-HT3 receptors in the central nervous system are involved in the gastric lesion formation by psychological stress. The stress was in a communication box paradigm, in which each 20 nonshocked mouse (responder) was placed in a Plexiglas compartment adjacent to mice receiving electrical shocks (sender). The responder mice revealed rather depressed gastric secretion, but developed gastric lesions which are significantly 25 attenuated by pretreatment of dl-p-chlorophenylalanine methyl ester:HCl (PCPA; 200-400 mg/kg p.o.), but not 6-hydroxydopamine (6-OH-DA; 60 micrograms/body i.c.v. or 80 mg/kg i.p. 1 hr after a 20-mg/kg i.p. dose of desipramine). Oral treatment 30 with GR38032F (0.01-1 mg/kg), ICS205-930 (0.01-20

mg/kg), MDL72222 (0.01-1 mg/kg), metoclopramide (0.1-100 mg/kg), ketanserin (0.01-10 mg/kg) and sulpiride (32-320 mg/kg) dose-dependently attenuated the psychological stress lesion formation; and the 5 activity was arranged in the order of their in vitro binding affinities for the 5-HT3, but not 5-HT1A or 5-HT2 receptors. In contrast, a peripherally acting 5-HT3 antagonist, M-840 ([[3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5-yl]-methyl]trimethyl-ammonium iodide), dopamine acting compounds, haloperidol and FR64822 [N-(4-pyridylcarbamoyl)amino-1,2,3,6-tetrahydropyridine], and antisecretory drugs, atropine and famotidine, minimally affected the lesion formation.

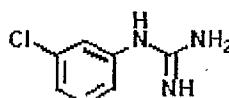
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- SDZ ICT 322, an indole-3-carboxylic acid scopoline ester
- MD-354

20

MD-354. We were intrigued by the novel 5-HT3 agonist phenylbiguanide. It seemed quite selective for 5-HT3 receptors, but displayed rather low affinity (Ki >1,000 nM). In a prior study with Dr. S. Peroutka, we had investigated the SAFIR of various aryl-piperazines at 5-HT3 receptors. Arylpiperazines, as mentioned earlier, are relatively nonselective agents; however, many bind at 5-HT3 receptors with significantly higher affinity than phenylbiguanide. We identified some structural similarities between the arylpiperazines and phenylbiguanide and, in collaboration with Milt Teitler, made a series of hybrid analogs that we hoped would bind with higher affinity than phenylbiguanide. Two such analogs were meta- chlorophenylbiguanide (*m*CPBG) and 2-naphthylbiguanide (Ki = 10-20 nM); both displayed significantly higher affinity than phenylbiguanide. Although we reported these compounds in abstract

form, a full paper <http://www.phc.vcu.edu/rag/serotonin/> - seven on mCPBG independently appeared by another group of investigators at the same time. It was not until a few years later that we finally published a full 5 paper on these agents. However, in the course of our studies, we identified a novel class of 5-HT3 agonists: the arylguanides. MD-354, for example, was found to bind at 5-HT3 receptors with high affinity (Ki ca. 35 nM) and to display agonist actions in 10 several assay systems.



15 MD-354

20 • S 21007 (21007 [5-(4-benzyl piperazin-1-yl)4H
pyrrolo [1,2-a]thieno[3,2-e]pyrazine]).

Interaction of S 21007 with 5-HT3 receptors. In vitro and in vivo characterization.

25 Delagrange P, Emerit MB, Merah N, Abraham C, Morain P, Rault S, Renard P, Pfeiffer B, Guardiola-LeMaitre B, Hamon M; *Eur J Pharmacol* 1996 Dec 5, 316:2-3:195-203

30 The interaction of S 21007 [5-(4-benzyl piperazin-1-yl)4H pyrrolo [1,2-a]thieno[3,2-e]pyrazine] with serotonin 5-HT3 receptors was investigated using biochemical, electrophysiological and functional assays. Binding studies using membranes from N1E-115 neuroblastoma cells showed that S 21007 is a 35 selective high affinity ($IC_{50} = 2.8$ nM) 5-HT3 receptor ligand. As expected of an agonist, S 21007 stimulated the uptake of [^{14}C]guanidinium (EC_{50}

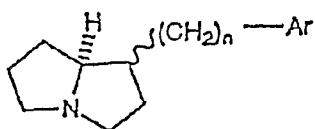
approximately 10 nM) in NG 108-15 cells exposed to substance P, and this effect could be prevented by the potent 5-HT3 receptor antagonist ondansetron. In addition, like 5-HT and other 5-HT3 receptor agonists (phenylbiguanide and 3-chloro-phenylbiguanide), S 21007 (EC50 = 27 microM) produced a rapid inward current in N1E-115 cells. The 5-HT3 receptor agonist action of S 21007 was also demonstrated in urethane-anaesthetized rats as this drug (120 micrograms/kg i.v.) triggered the Bezold-Jarisch reflex (rapid fall in heart rate), and this action could be prevented by pretreatment with the potent 5-HT3 receptor antagonist zacopride. Finally, in line with its 5-HT3 receptor agonist properties, S 21007 also triggered emesis in the ferret. Evidence for 5-HT3 receptor antagonist-like properties of S 21007 was also obtained in some of these experiments since previous exposure to this compound prevented both the 5-HT-induced current in N1E-115 cells and the Bezold-Jarisch reflex elicited by an i.v. bolus of 5-HT (30 micrograms/kg) in urethane-anaesthetized rats. These data suggest that S 21007 is a selective 5-HT3 receptor agonist which can exhibit antagonist-like properties either by triggering a long lasting receptor desensitization or by a partial agonist activity at 5-HT3 receptors in some tissues.

Further, in the following patent publications more compounds useful according to the present invention are presented.

N-substituted benzamides

• EP0417746 (September 1990, G.D. Searle & Co) *N*-Aza-bicyclo/3.3.0/octane amides of aromatic acids. See
5 also US5126343.

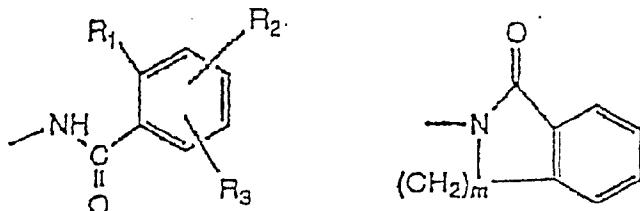
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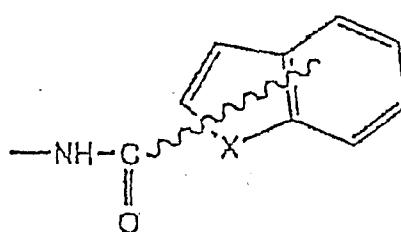
or a pharmaceutically acceptable salt thereof
wherein n is 0 or 1;
Ar can be

20

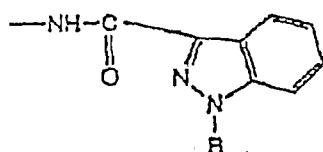


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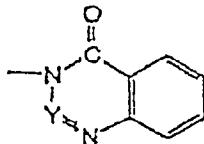
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R^1 is alkoxy of 1 to 6 carbon atoms; and
 R^2 and R^3 are the same or different and are
hydrogen, halogen, CF_3 , hydroxy, C_{1-6} alkoxy, C_{2-7}
acryl, amino, amino substituted by one or two C_{1-6}
alkyl groups, C_{2-7} acylamino, aminocarbonyl or
aminosulfone, optionally substituted by one or two
 C_{1-6} alkyl groups, C_{1-6} alkyl sulfone or nitro
groups; wherein X can be NR, S, or O;
Y can be CH or N;
R is H, alkyl or aryl; and
m is 1 or 2.

The structure is a benzamide with $Ar=Ph-CONH-$.

A compound of the formula or a pharmaceutically
acceptable salt thereof wherein n is = or 1; and Ar
is an aromatic amide moiety, which compound exhibits
prokinetic activity and is a 5-HT3 antagonist.

- EP0430190 (November 1990, Syntex, Inc) New tricyclic compounds in which
the dashed line denotes an optional double bond;
n is 1, 2 or 3;
- p is 0, 1, 2 or 3;
- q is 0, 1 or 2;

each R^1 is independently selected from halogen, hydroxy, lower C_{1-6} alkoxy (optionally substituted with phenyl), lower C_{1-6} alkyl, nitro, amino, amino-carbonyl, (lower C_{1-6} alkyl)amino, di(lower C_{1-6} alkyl)amino, and (lower C_{1-6} alkanoyl)amino;

5 each R^2 is lower C_{1-6} alkyl; and

R^3 is selected from

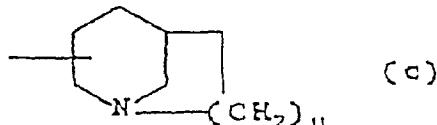
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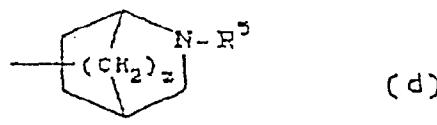
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25



30

in which

u , x , y and z are all independently an integer from 1 to 3; and

35 R^4 and R^5 are independently C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-2} alkyl, or a group $(CH_2)_t R_6$ where t is 1 or 2 and R_6 is thiienyl,

pyrrolyl or furyl optionally further substituted by one or two substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C₁₋₄ alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C₁₋₄ alkyl (optionally substituted by hydroxy, C₁₋₄ alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy); or

10 a pharmaceutically acceptable salt thereof or an N-oxide thereof; or

an individual isomer or mixture of isomers thereof.

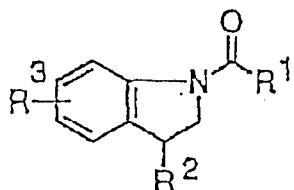
The present invention is directed to new pharmaceutically active compounds with 5-HT₃ receptor antagonist activity of Formula I: in which the dashed line denoted an optional double bond; n is 1, 2 or 3; p is 0, 1, 2 or 3; q is 0, 1 or 2; each R₁ is halogen, hydroxy, alkoxy (optionally substituted with phenyl), alkyl, nitro, amino, amino carbonyl, (alkyl)amino, di(alkyl)amino, and (alkanoyl)amino; each R² is alkyl; and R₃ is in which u, x, y and z are all independently an integer from 1 to 3; and R₄ and R₅ are independently alkyl, cycloalkyl, cycloalkylalkyl, or a group (CH₂)_tR₆ where t is 1 or 2 and R₆ is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from alkyl, alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and alkyl (optionally substituted).

Indoles, Indole-1-carboxamides and Imidazole derivatives

- EP0721949 (September 1993, Tokyo Tanabe Coompany Limited) Indoline compound and 5-HT3 receptor antagonist containing the same as active ingredient.

5

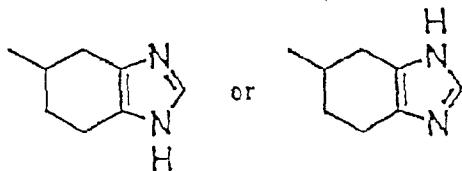
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15

wherein R¹ represents the group

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30

R² represents a phenyl group which may be substituted or an aromatic heterocyclic group, and R³ represents hydrogen, a halogen, or a lower alkyl group, hydroxyl group, lower alkoxy group, carbamoyl group or lower alkoxy carbonyl group, or a physiologically acceptable salt thereof, or its solvate.

35

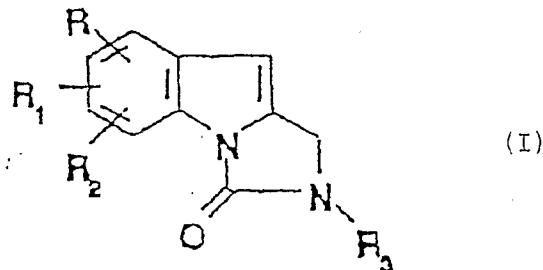
An indoline compound represented by general formula (I); a physiologically acceptable salt thereof; solvates of these compounds; and a 5-HT3 receptor antagonist containing the same as the active ingredient. In formula (I) R¹ represents the group (a) or (b),

R₂ represents optionally substituted phenyl or heteroaryl; and R₃ represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, carbamoyl or lower alkoxy carbonyl. The compound has a potent antagonism against 5-HT₃ receptors in the intestinal tract as compared with the known 5-HT₃ receptor antagonists and is excellent in the persistence of the activity. Hence it is useful for preventing or treating vomiting or nausea induced by chemotherapy or radiation, irritable bowel syndrome and diarrhea.

- EP0711299 (May 1994, Pharmacia S.p.A) Azabicycloalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One As 5HT 3 Antagonists

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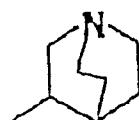
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wherein

each of R, R₁ and R₂, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C₁-C₆ alkyl, CF₃, C₁-C₆ alkoxy, C₁-C₆ alkylthio, formyl, C₂-C₆ alkanoyl, carboxy, C₁-C₆ alkoxy carbonyl, nitro, -N(R₄ R₅) in which each of R₄ and R₅ independently is hydrogen, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl; or a (R₆ R₇)N-SO₂ group, in which each of R₄ and R₇ independently is hydrogen or C₁-C₆ alkyl; R₃ is a group a)

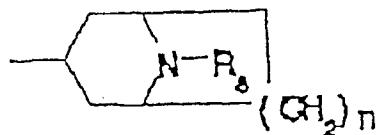
35



90

or b)

5



10

wherein

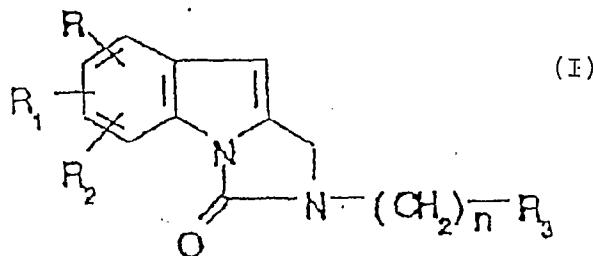
n is an integer of 1 or 2 and R₈ is hydrogen, C₁-C₆ alkyl unsubstituted or substituted by phenyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, formyl or C₂-C₆ alkanoyl; and the pharmaceutically acceptable salts thereof.

15

Novel 5-HT₃ receptor antagonist compounds having general formula (I) wherein each of R, R₁ and R₂, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C₁-C₆ alkyl, CF₃, C₁-C₆ alkoxy, C₁-C₆ alkylthio, formyl, C₂-C₆ alkanoyl, carboxy, C₁-C₆ alkyl-carbonyl, nitro, -N(R₄ R₅) in which each of R₄ and R₅ independently is hydrogen, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl; or a (R₆ R₇)N-SO₂ group, in which each of R₆ and R₇ independently is hydrogen or C₁-C₆ alkyl; R₃ is a group (a) or (b) wherein n is an integer of 1 or 2 and R₈ is hydrogen, C₁-C₆ alkyl unsubstituted or substituted by phenyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, formyl or C₂-C₆ alkanoyl; and the pharmaceutically acceptable salts thereof, are provided.

- EP0711293 (May 1994, Pharmacia S.p.A) Imidaxolylalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One And Their Use As Therapeutic Agents.

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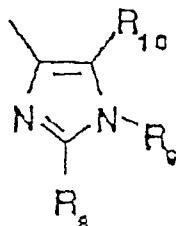
wherein

n, 1, 2 or 3 is;

10 each of R, R₁ and R₂, which may be the same or different, is hydrogen, halogen, hydroxy, cyano C₁-C₆ alkyl, CF₃, C₁-C₆ alkoxy, C₁-C₆ alkylthio, formyl, C₂-C₆ alkanoyl, carboxy, C₁-C₆ alkoxy carbonyl, nitro, -N(R₄)R₅ in which each of R₄ and R₅ independently is hydrogen, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl; or a R₆(R₇)N-SO₂ group, in which each of R₆ and R₇ independently is hydrogen or C₁-C₆ alkyl;

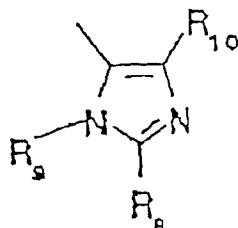
15 R₃ is an imidazolyl group having the formula
a)

20



25

or b)



35

wherein each of R₆ and R₁₀, which may be the same or different, is hydrogen or C₁-C₆ alkyl, R₉ is hydrogen, C₁-C₆ alkyl or a nitrogen protection group chosen from triphenylmethyl, t-butyloxycarbonyl,

benzyloxycarbonyl, acetyl, formyl, di(p-methoxyphenyl)methyl and (p-methoxyphenyl)diphenylmethyl;
and the pharmaceutically acceptable salts thereof.

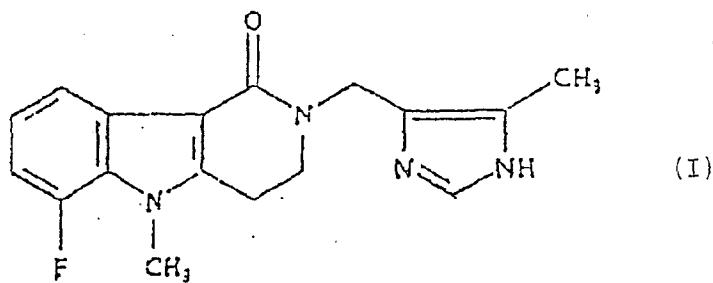
5

Novel 5-HT3 receptor antagonist compounds having formula (I), wherein n is 1, 2 or 3; each of R, R1 and R2, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C1-C6 alkyl, CF3, C1-C6 alkoxy, C1-C6 alkylthio, formyl, C2-C6 alkanoyl, carboxy, C1-C6 alkoxy-carbonyl, nitro, -N(R4 R5), in which each of R4 and R5 independently is hydrogen, C1-C6 alkyl, formyl or C2-C6 alkanoyl; or a (R6 R7)N-SO2 group, in which each of R6 and R7 independently is hydrogen or C1-C6 alkyl; R3 is an imidazolyl group of formula (a) or (b), wherein each of R8 and R10 which may be the same or different is hydrogen or C1-C6 alkyl, R9 is hydrogen, C1-C6 alkyl or a nitrogen protecting group; and the pharmaceutically acceptable salts thereof, are disclosed.

- EP0581388 (July 1993, Glaxo Group Ltd) Pyridoindolone Methansulphonate as 5HT and 5HT3 receptor antagonists.

25

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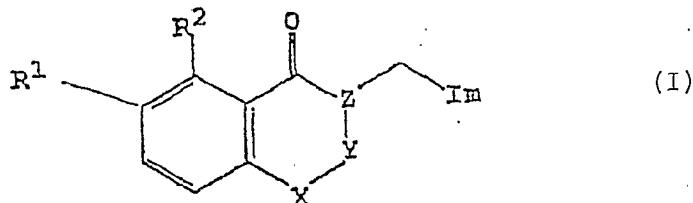
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This invention relates to the novel salt 6-fluoro-2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one methane sulfonate, to solvates of this salt, to pharmaceutical

compositions containing it and to its use in medicine as 5-HT3 receptor antagonists.

5 • EP0364274 (October 1989, Glaxo Group Ltd) Imidazole derivatives.

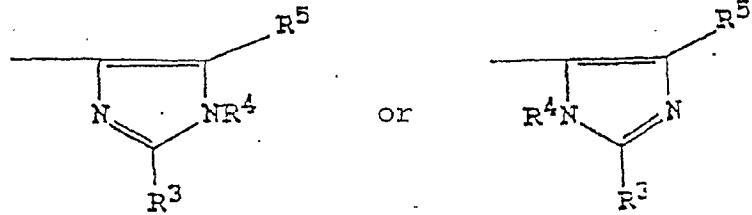
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wherein Im represents an imidazolyl group of the formula:

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25

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and one of the groups represented by R³, R⁴ and R⁵ is a hydrogen atom, or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, phenyl or phenyl C₁₋₃ alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group;

35

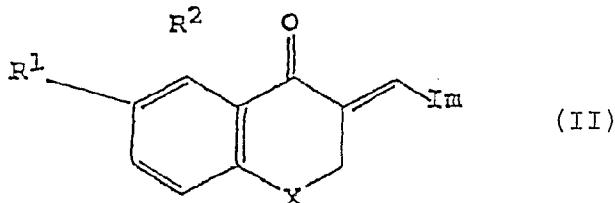
R¹ and R² each represent a hydrogen atom, or together with the carbon atoms to which they are attached form a phenyl ring;

X represents an oxygen or a sulphur atom, or a group NR⁶, wherein R⁶ represents a C₁₋₆ alkyl group;

Z-Y represents the group CH-CH₂ or C=CH;
and physiologically acceptable salts and solvates,
thereof, which comprises:

5 (A) for the production of a compound of formula (I)
in which Z-Y represents the group CH-CH₂,
hydrogenating a compound of formula (II):

10



15

or a protected derivative thereof, followed if necessary by removal of any protecting groups present; or

20

(B) for the production of a compound of formula (I)
in which Z-Y represents the group C=CH, reacting a compound of formula (II), or a protected derivative thereof, with an organic acid or a mineral acid, followed if necessary by removal of any protecting groups present; or

(C) converting a compound of general formula (I)
into another compound of formula (I) using conventional techniques; or

25

(D) removing protecting group(s) from a protected form of a compound of formula (I);
and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer;

30

and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

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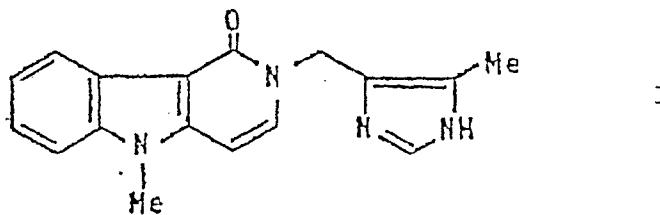
The invention provides imidazole derivatives of the general formula (I) wherein Im represents an imidazolyl group of the formula: and one of the groups represented by R₃, R₄ and R₅ is a hydrogen atom, or

5 a C1-C6 alkyl, C3-7 cycloalkyl, C3-6 alkenyl, phenyl or phenyl C1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C1-6 alkyl group; R1 and R2 each represent a hydrogen atom, or together with the carbon atoms to which they are attached form a phenyl ring; X represents an oxygen or a sulphur atom, or a group NR₆, wherein R₆ represents a C1-6 alkyl group; Z-Y represents the group CH-CH₂ or C=CH; and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine at 5-HT₃ receptors and are useful, for example, in the treatment of psychotic disorders, anxiety and nausea and vomiting.

- EP0392663 (March 1989, One Pharmaceutical Co Ltd)
Carboline derivative as a 5-HT₃ receptor antagonist.

20 A γ -carboline of the formula I

25



30

or pharmaceutically acceptable acid addition salt and/or hydrate thereof for use in a method of treatment or prophylaxis of diseases or conditions induced by the action of 5-hydroxytryptamine on 5-hydroxytryptamine 3-receptors in a mammal, including man.

35

The present invention provides γ -carbolines of the formula: or non-toxic acid additional salts thereof

and/or hydrates thereof, for use as 5-HT3 receptor antagonists. The present invention also provides pharmaceutical compositions comprising compounds of the formula I.

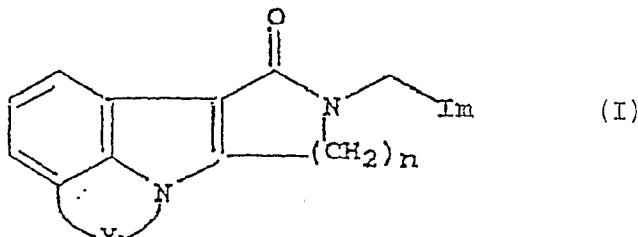
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- EP0357417 (August 1989, Glaxo Group Ltd) Lactam derivatives.

Compounds of the general formula (I)

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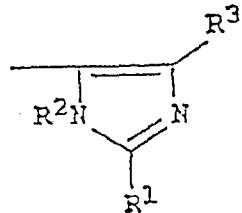
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wherein n represents 2 or 3;

Im represents an imidazolyl group of the formula:

25

or



30

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wherein one of the groups represented by R¹, R² and R³ is a hydrogen atom or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, phenyl or phenyl C₁₋₃ alkyl- group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group;

Y represents a group $-(CH_2)_m-$, wherein m represents 2, 3 or 4; or Y represents a group $-X(CH_2)_p-$, C₁₋₆ alkyl group, and X is attached to the benzene ring moiety of the molecule;

5 and physiologically acceptable salts and solvates thereof.

The invention provides lactam derivatives of the general formula (I) wherein n represents 2 or 3; I_m represents an imidazolyl group of the formula:

10 wherein one of the groups represented by R₁, R² and R₃ is a hydrogen atom or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, phenyl or phenyl C₁₋₃ alkyl-group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group; Y represents a group $-(CH_2)_m-$, wherein m represents 2, 3 or 4; or Y

15 represents a group $-X(CH_2)_p-$, wherein p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR₄, where R₄ is a C₁₋₆ alkyl group, and X is attached to the benzene ring moiety of the molecule;

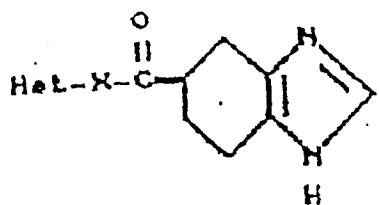
20 and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine at 5-HT₃ receptors and are useful, for example in the treatment of psychotic disorders, anxiety and nausea and vomiting.

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30 • RU2059623 Tetrahydrobenzimidazole derivatives or its pharmaceutically acceptable salt.

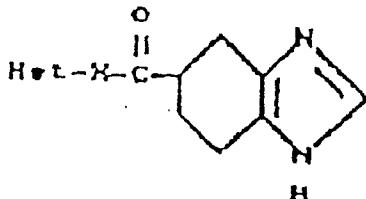
tetrahydrobenzimidazole derivative of the formula

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and a pharmaceutical

composition containing an effective amount of compound



and a pharmaceutically

acceptable carrier showing activity of a 5-HT₃ receptor antagonist.

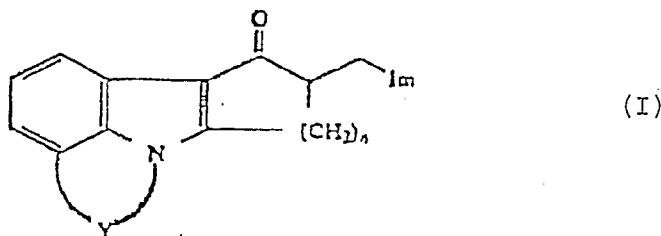
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- US5,045,545 (May 1989, Glaxo Group Limited) [(Imidazol-4 (and 5)-yl)methyl] tetracyclic ketones having 5-HT₃ antagonist activity.

15

The invention relates to tetracyclic ketones of the general formula (I)

20



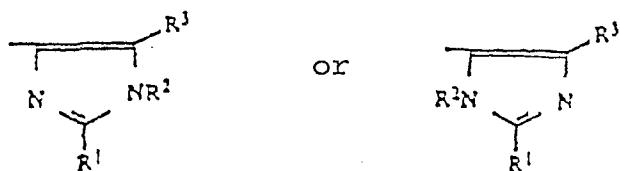
wherein

n represents 1, 2 or 3;

25

Im represents an imidazolyl group of the formula:

30



35

wherein one of the groups represented by R¹, R² and R³ is a hydrogen atom or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, phenyl or phenyl C₁₋₃ alkyl group, and each of the other two groups, which

may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group;
Y represents a group -(CH₂)_m-, wherein m represents 2, 3 or 4; or a group -X(CH₂)_p-, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR⁴, where R⁴ is a C₁₋₆ alkyl group, and X is attached to the benzene ring moiety of the molecule;
and physiologically acceptable salts and solvates thereof.

15 The compounds are potent and selective antagonists of the effect of 5-HT₃ receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

20 The invention relates to tetracyclic ketones of the general formula (I)##STR1## wherein n represents 1, 2 or 3; Im represents an imidazolyl group of the formula: ##STR2## wherein one of the groups represented by R.¹, R.² and R.³ is a hydrogen atom or a C₁₋₆ alkyl, C₁₋₇ cycloalkyl, C₃₋₆ alkenyl, phenyl or phenyl C₁₋₃ alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group; Y represents a group -(CH₂)_m-, where m represents 2, 3 or 4, or a group -
25 X(CH₂)_p-, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR⁴, where R⁴ is a C₁₋₆ alkyl group, and X is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof. The compounds are potent and
30 selective antagonists of the effect of 5-HT at 5-HT₃ receptors and are useful, for example, in
35

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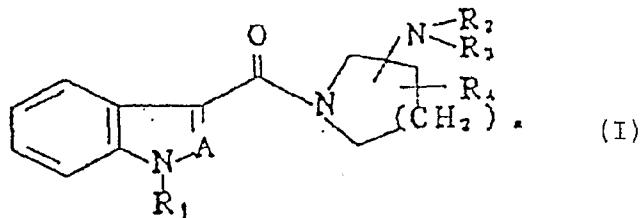
the treatment of psychotic disorders, anxiety, and nausea and vomiting.

Indazole carboxamide derivatives

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- EP0630893 (March 1992, Kyorin Pharmaceutical Co., Ltd.) N,N'-Disubstituted Amide Derivative.

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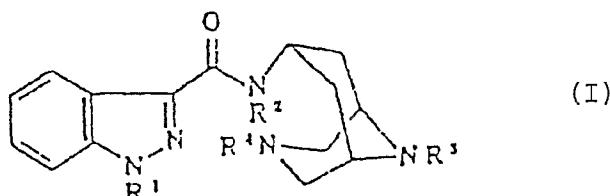
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A 5-HT3 antagonist containing a novel N,N'-disubstituted amide derivative having a potent and selective 5-HT3 receptor antagonism, represented by general formula (I), a hydrate thereof, or an acid addition salt thereof, wherein R1 represents hydrogen or lower alkyl; R2 and R3 may be the same or different from each other and each represents hydrogen, lower alkyl, lower alkenyl, aryl-substituted lower alkyl which may be substituted, acyl or lower alkoxy carbonyl; R4 represents hydrogen, lower alkyl or lower alkoxy; A represents CH or N; and n represents 1, 2 or 3.

- EP0558923 (January 1992, Nisshin Flour Milling Co., Ltd.) Diazabicyclo derivatives as 5-HT3 antagonists

30

35



wherein

R¹ is alkyl, 3-methyl-2-butenyl, cyclopropylmethyl, 2-propynyl, cyanomethyl, 2-oxopropyl, 2-hydroxypropyl, 2-pyridylmethyl, methoxycarbonylmethyl, 2-ethoxyethyl, isobutoxycarbonyl, or 4,6-diamino-2-triazinylmethyl;
5 R² is hydrogen; and
R³ and R⁴ are methyl.

10 Diazabicyclo derivatives of formula (I) and pharmaceutically acceptable salts thereof: wherein R¹ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, oxoalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, acyl, dialkylaminoalkyl, hydroxyalkyl, haloalkyl, cyanoalkyl, heterocycloalkyl, aryl, heteroarylalkyl or arylalkyl, the aryl group and the aryl moiety being optionally substituted by alkoxy, nitro, alkyl, amino or halo; R² is hydrogen or alkyl; R³ and R⁴ may be the same or different and each is hydrogen, alkyl, alkenyl, acyl, alkoxyalkyl or arylalkyl wherein the aryl moiety is optionally substituted by alkoxy, nitro, alkyl, amino or halo; with the proviso that when R² is hydrogen and both R³ and R⁴ are methyl, R¹ does not represent hydrogen, alkyl, unsubstituted benzyl or dimethylaminoethyl; having 5-HT3 receptor antagonist activity.

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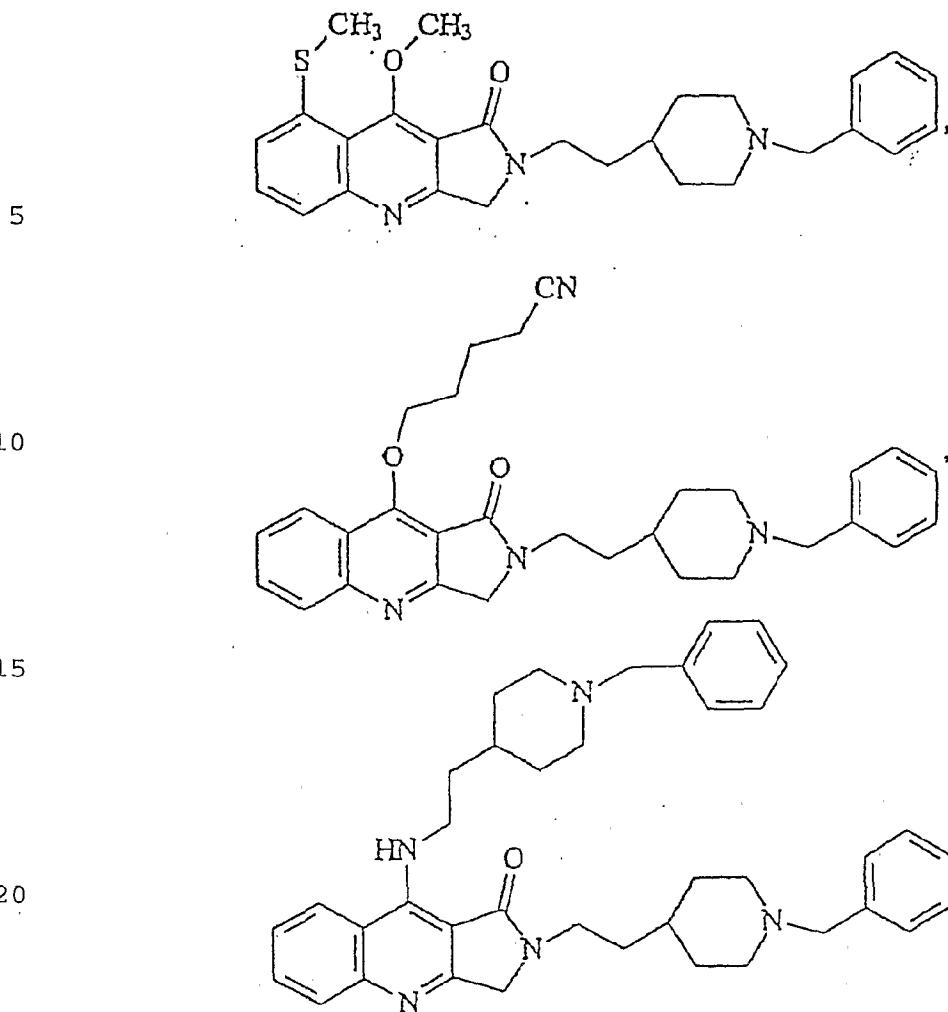
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30 *Quinolines and Isoquinolines*

- WO9964421 (June 1999, Arena Pharmaceuticals, Inc)
Acetylcholine enhancers.

35 An acetylcholine enhancer selected from the group consisting of the chemical compounds represented by the following structures:

102

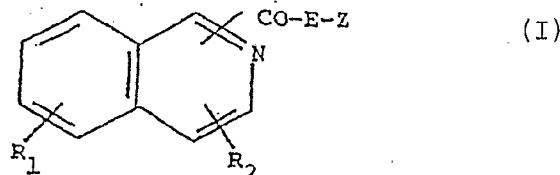


Disclosed herein are quinoline derivatives having
 25 dual mechanistic properties, referred to in this
 patent documents as "acetylcholine enhancers", i.e.,
 compounds which evidence acetylcholinesterase (AChE)
 inhibition activity, and 5-HT3 receptor antagonist
 activity. A particularly preferred compound is 2-[2-
 30 (1-benzylpiperizin-4-yl)ethyl]-2,3-dihydro-9-methoxy-
 1H-pyrrolo[3,4-b]quinolin-1-one hemifumarate,
 referred to herein as Compound A ("Cm.A").

- EP0526545 (April 1991, Beecham Group p.l.c.)
 35 Isoquinoline Amides And Esters As 5-HT3 Receptor
 Antagonists.

A compound of formula (I), or a pharmaceutically acceptable salt thereof:

5



10

wherein

E is NH or O,

R₁ is hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, hydroxy or nitro;

15 Z is an azacyclic or azabicyclic side chain; and

i) the group CO-E-Z is in the 1-position and either R₂ is in the 3-position and is hydrogen, C₁₋₆ alkyl or C₁₋₆ alkoxy, or R₂ is in the 4-position and is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₇ acyl, C₁₋₇ acylamino, phenyl

20 optionally substituted by one or two C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C₁₋₆ alkyl or C₃₋₈ cycloalkyl groups or by C₄₋₅ polymethylene or by phenyl, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylsulphanyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, hydroxy or nitro; or

25

ii) the group CO-E-Z is in the 3-position and either R₂ is in the 1-position and is hydrogen, C₁₋₆ alkyl or C₁₋₆ alkoxy, or R₂ is in the 4-position and is hydrogen or C₁₋₆ alkoxy;

30

35 having 5-HT₃ receptor antagonist activity.

104

Isoquinoline derivatives (I) having 5-HT3 receptor antagonist activity, a process for their preparation and their use as pharmaceuticals. In formula (I) E is NH or O, R1 is hydrogen, halogen, alkyl, alkoxy, hydroxy or nitro; Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c) wherein; p is 1 or 2; q is 1 to 3; r is 1 to 3; R3 or R4 is hydrogen or alkyl, and Y is a group -CH2-X-CH2- wherein X is -CH2-, oxygen, sulphur or X is a bond; and (I) when the group CO-E-Z is in the 1-position and either R2 is in the 3-position and is hydrogen, alkyl, or alkoxy, or R2 is in the 4-position and is hydrogen CF3, alkyl, acyl, acylamino (substituted) phenyl or (substituted) amino, (substituted) aminocarbonyl or (substituted) aminosulphonyl; (II) the group CO-E-Z is in the 3-position and either R2 is in the 1-position and is hydrogen, alkyl or alkoxy or R2 is in the 4-position and is hydrogen or alkoxy.

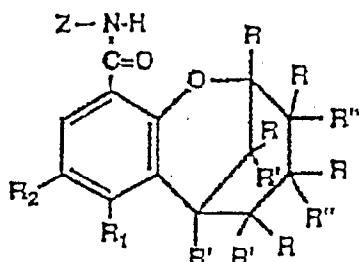
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- EP0628043 (February 1992, Merrell Dow Pharmaceutical Inc) 2,6-Methano-2H-Quinolizin As 5-HT3-Receptor Antagonist

25

A compound of the formula:

30



35

where

R is hydrogen or alkyl;

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R₁ is hydrogen, amino, mono- and di-alkylamino, acylamino, halo or haloalkyl;

R₂ is hydrogen, halo, sulfamyl, mono- and di-alkylsulfamyl or haloalkyl;

5 R' and R" are independently hydrogen or alkyl;

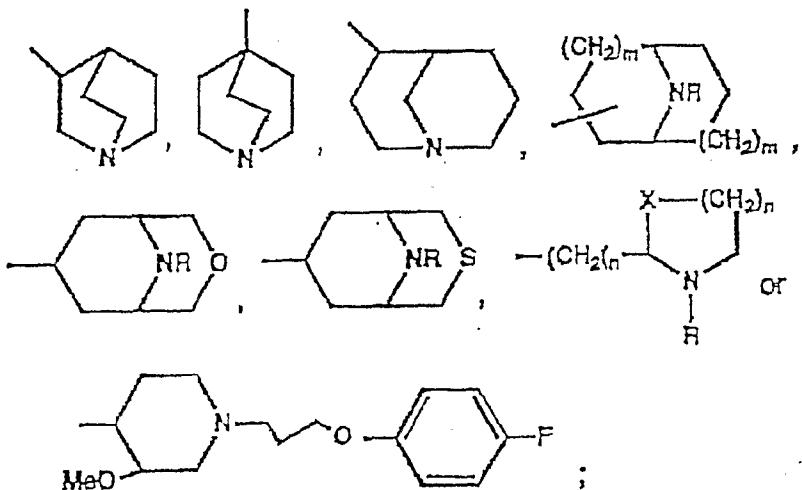
vicinal R' and/or R" groups may form a C=C double bond;

geminal R and R' and R and R" groups may be -(CH₂)_n- where n is 2 to 6;

10

Z is

15



20

25

30

where m is 0-2, n is 1-2 and X is N or S; or pharmaceutically acceptable salts thereof.

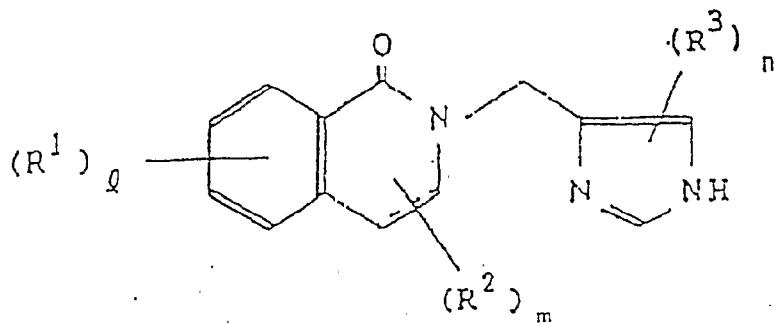
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This invention relates to 5-chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acid-octahydro-3-hydroxy-2,6-methano-2H-quinolizin-8-yl ester (I), a novel 5-HT₃-receptor antagonist, its method of preparation, and to its end-use application in the

5 treatment of radio- and chemo-therapeutically-induced nausea and vomiting, in the treatment of pain associated with migraine, in the treatment of cognitive disorders, in treating hallucinatory endogenous psychoses of the type manifested in patients suffering from schizophrenia and mania, for irritable bowel syndrome, and to combat drug abuse.

10 • EP0482939 (October 1991, Ono Pharmaceuticals)
Isoquinolinone derivative.

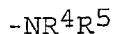
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wherein each substituent R¹ is the same or different and is hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy or a group of formula:



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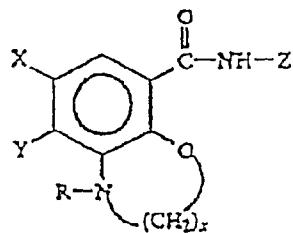
wherein R⁴ is hydrogen, C₁₋₄ alkyl or C₂₋₄ alkanoyl and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl; each substituent R² is the same or different and is hydrogen or C₁₋₄ alkyl; each substituent R³ is the same or different and is hydrogen or C₁₋₄ alkyl; l is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2 and

== is a single bond or double bond; or a non-toxic acid addition salt thereof or a hydrate thereof.

Isoquinolinone derivatives of the formula: wherein
5 R1 is hydrogen, C1-4 alkyl, C1-4 alkoxy or a group
of formula: -NR4R5 wherein R4 is hydrogen, halogen,
C1-4 alkyl or C2-4 alkanoyl and R5 is hydrogen, C1-4
alkyl or benzyl; R² is hydrogen or C1-4 alkyl; R3 is
hydrogen or C1-4 alkyl; 1 is 1, 2, 3 or 4; m is 1 or
10 2; n is 1 or 2 and --- is a single bond or double
bond an non-toxic acid addition salts thereof and
are useful for the prevention and/or treatment of
diseases induced when 5-HT acts on 5-HT₃ receptors
15 (especially vomiting induced by the administration
of an anti-cancer agent).

Benzofuranes, Benzooxazines and Benzo(di)azepines

- US4935511 (September 1989, Rorer Pharmaceutical Corporation) Benzoxazine benzooxazipine carboxamide 5-HT3 antagonists.



30

where

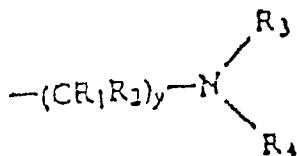
X is hydrogen, halo, sulfamyl, alkylsulfamyl or alkylsulfonyl;

Y is hydrogen, amino, mono- or di-alkylamino or halo;

108

Z is

5



10 3-quinuclidine, 4-quinuclidine, 4-(1-azabicyclo-[3.3.1]nonane), 3-(9-methylazabicyclo[3.3.1]nonane) or 4-[3-methoxy-1-(3(-[4-fluorophenoxy]propyl)piperidine];

15 R, R₁, R₂, R₃ and R₄ are independently: hydrogen or alkyl;

x is 2 or 3;

y is 1 to 4;

and pharmaceutically acceptable salts thereof.

20 This invention relates to benzoxazine and benzoxazepine carboxamide compounds which exhibit 5-HT₃ antagonist properties including CNS, anti-emetic and gastric prokinetic activity and which are void of any significant D₂ receptor binding affinity. This invention also relates to pharmaceutical compositions and methods for the treatment of gastrointestinal and mental disorders using said compounds.

25 30 • IL 107654 Use of substituted N-3,4-dihydro-4-oxo-2-2-pyrimidyl)amino alkyl-4-piperidinyl 2,2-dimethyl-7-benzofuran and benzopyrancarboxamide.

35 A pharmaceutically acceptable acid addition salt form or a stereochemically isomeric form thereof, wherein R₁ and R₂ represent hydrogen, or

R1 and R2 taken together from a bivalent radical of formula

-CH=CH-CH=CH- (a)

-CH=C(Cl)-CH=CH- (b) or

-CH=CH-C(Cl)=CH- (c);

n represents 2, 3 or 4;

R3 represents hydrogen or methoxy;

m represents 1 or 2;

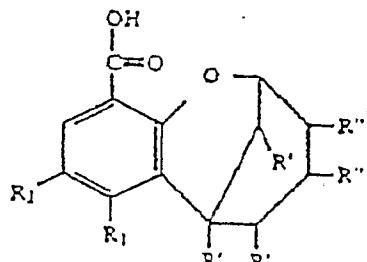
10 R4 represents hydrogen, amino or C1.3alkylcarbonyl-amino; and

R5 represents hydrogen or halo,

for the manufacture of a medicament for treating 5-HT3-mediated disorders.

15 • US5288731 (August 1992, Rhone-Poulenc Rorer Pharmaceuticals Inc) 2,6-Methano-2H-1-Benzoxacincarboxylic acids, esters and amides.

20



25

and its stereoisomers, enantiomers, diastereoisomers and racemic mixtures with an amine of the formula

30 H2N-Z;

where

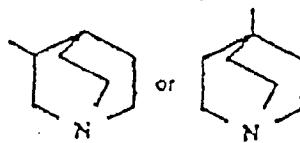
R1 is hydrogen, an amino or alkylamino optionally substituted with a protecting group halo or haloalkyl;

35 R2 is hydrogen, halo, sulfamyl, mono- and di-alkylsulfamyl or haloalkyl;

R' and R'' are hydrogen or alkyl; and Z is:

110

5



and its racemic mixtures and stereospecific isomers.

10 Novel compounds which are 2,6-methano-2H-1-benzoxazin-3-ones having 5-HT₃-antagonist properties including unique CNS, antiemetic and gastric prokinetic activities and which are void of any significant D₂ receptor binding affinity, 15 therapeutic compositions and methods of treatment of disorders which result from 5-HT₃ activity using said compounds. Processes for their preparation and the preparation of their intermediates are also disclosed.

20

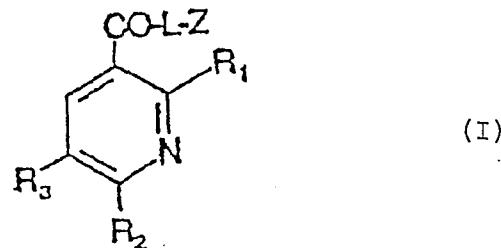
- WO9209284 2,6-Methano-2H-1-benzoxazin-3-ones as 5-HT₃ antagonists.

25 *Other 5-HT₃ antagonist compounds*

- EP0611370 (October 1992, Smithkline Beecham Plc) Pyridine-3-Carboxylic Acid Esters Or Amides Useful As 5-HT₃ Antagonists.

30 A compound of formula (I), or a pharmaceutically acceptable salt thereof:

35



wherein

5 R₁ is C₁₋₆ alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cyclo-alkyl C₁₋₄ alkoxy;

R₂ is hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino optionally substituted by one or two C₁₋₆ alkyl groups;

10 R₃ is hydrogen, halo or C₁₋₆ alkyl;

L is O or NH; and

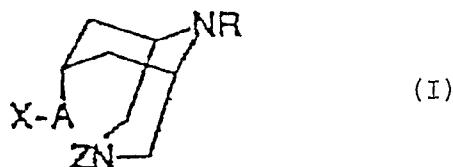
Z is a di-azacyclic or azabicyclic side chain; having 5-HT₃ receptor antagonist activity.

15 Compounds of formula (I) and pharmaceutically acceptable salts thereof wherein R₁ is C₁₋₆ alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cycloalkyl C₁₋₄ alkoxy; R₂ is hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino optionally substituted by one or two C₁₋₆ alkyl groups; R₃ is hydrogen, halo or C₁₋₆ alkyl; L is O or NH; and Z is a di-azacyclic or azabicyclic side chain; having 5-HT₃ receptor antagonist activity.

20 • EP0607233 (October 1991, Smithkline Beecham Plc) 3,9-Diazabicyclo(3.3.1)Nonane Derivatives With 5-HT₃ Receptor Antagonist Activity

25 A compound of formula (I), or a pharmaceutically acceptable salt thereof:

30



35

wherein

X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

5 A is a linking moiety;

Z is a carboxylic acyl group; and

R is hydrogen or methyl;

having 5-HT₃ receptor antagonist activity.

10

Compounds of formula (I), and pharmaceutically acceptable salts thereof, wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is a linking moiety; Z is a carboxylic acyl group; and R is hydrogen or methyl;

15 having 5-HT₃ receptor antagonist activity.

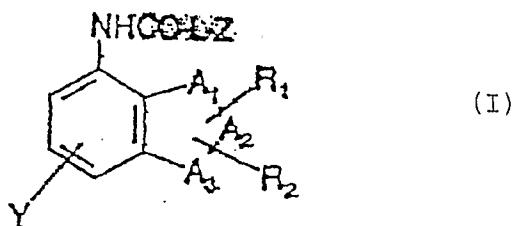
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- WO9308185 (January 1991, Smithkline Beecham Plc) N-Aryl-N¹-Azabicyclo-Ureas As 5-HT₃ Antagonists

A compound of formula (I) or a pharmaceutically acceptable salt thereof:

25

30



wherein

A₁, A₂, A₃ and the carbon atoms to which they are attached form a 5- or 6-membered non-aromatic heterocyclic ring containing at least one -O-, -CO- or -N-;

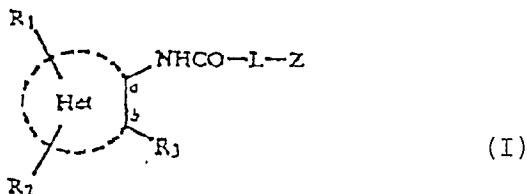
R₁ and R₂ are hydrogen or C₁₋₆ alkyl;
 Y is hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ alkoxy;
 L is O or NH;
 Z is an azabicyclic side chain;
 5 having 5-HT₃ receptor antagonist activity.

Compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein A₁, A₂, A₃ and the carbon atoms to which they are attached form a
 10 5- or 6-membered non-aromatic heterocyclic ring containing at least one -O-, -CO- or -N-; R₁ and R₂ are hydrogen or C₁₋₆ alkyl; Y is hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ alkoxy; L is O or NH; Z is an
 15 azabicyclic side chain; having 5-HT₃ receptor antagonist activity.

- US4808588 (July 1987, Beecham Group) Heterocyclic ureas and carbonates useful as pharmaceuticals.

20

25



wherein

Het is monocyclic heteroaryl having two adjacent carbon atoms, a and b, depicted in formula (I) selected from the group consisting of pyridine, pyrimidine, pyrazine, pyrrole, imidazole, thiophene, furan, oxazole and thiazole;
 30 R₁ and R₂ are independently selected from hydrogen, halogen, CF₃, C₁₋₆ alkyl and C₁₋₆ alkoxy;
 35 R₃ is hydroxy, C₁₋₆ alkoxy, C₃₋₇ alkenyl-methoxy, phenoxy or phenyl C₁₋₄ alkoxy in which either phenyl

moiety may be substituted by one or two C₁₋₆ alkyl, C₁₋₆ alkoxy or halo; CO₂R₆ wherein R₆ is hydrogen or C₁₋₆ alkyl, CONR₇R₈ or SO₂NR₇R₈ wherein R₇ and R₈ are independently hydrogen or C₁₋₆ alkyl or together are C₄₋₆ polymethylene, NO₂, (CH₂)_mOR₉ wherein m is 1 or 2 and R₉ is C₁₋₆ alkyl or S(O)_nR₁₀ wherein n is 0, 1 or 2 and R₁₀ is C₁₋₆ alkyl;

5 L is NH or O;

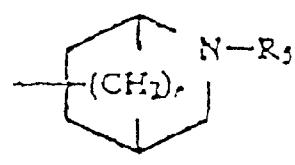
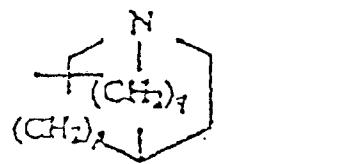
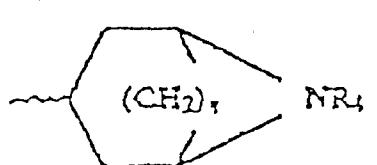
Z is a group of formula (a), (b) or (c):

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30 wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R₄ or R₅ is C₁₋₄ alkyl.

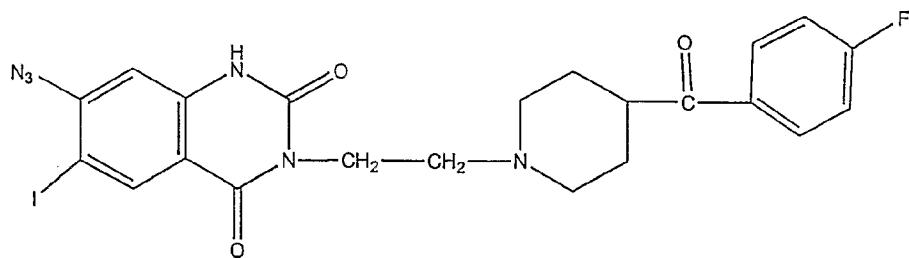
35 Compounds of formula (I), or a pharmaceutically acceptable salt thereof: ##STR1## wherein: Het is monocyclic heteroaryl having two adjacent carbons atoms, a and b, depicted in formula (I); p₁ R._{sub.1} and R._{sub.2} are independently selected from

hydrogen, halogen, CF₃sub.3, C₁sub.1-6 alkyl and C₁sub.1-6 Alkoxy; R₃sub.3 is hydroxy, C₁sub.1-6 alkoxy, C₁sub.3-7 alkenyl-methoxy, phenoxy or phenyl C₁sub.1-4 alkoxy in which either phenyl moiety may be substituted by one or two C₁sub.1-6 alkyl, C₁sub.1-6 alkoxy or halo; C₂sub.2 R₆ wherein R₆ is hydrogen or C₁sub.1-6 alkyl, CONR₇sub.7 R₈ or SO₂sub.2 NR₇sub.7 R₈ wherein R₇ and R₈ are independently hydrogen or C₁sub.1-6 alkyl or together are C₁sub.4-6 polymethylene, NO₂sub.2, (CH₂sub.2)_m OR₉ wherein m is 1 or 2 and R₉ is C₁sub.1-6 alkyl or S(O)_n R₁₀ wherein n is 0, 1 or 2 and R₁₀ is C₁sub.1-6 alkyl; L is NH or O; Z is a group of formula (a), (b) or (c); ##STR2## wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R₄ or R₅ is C₁sub.1-4 alkyl; having 5-HT₃ antagonist activity, a process for their preparation and their use as pharmaceuticals.

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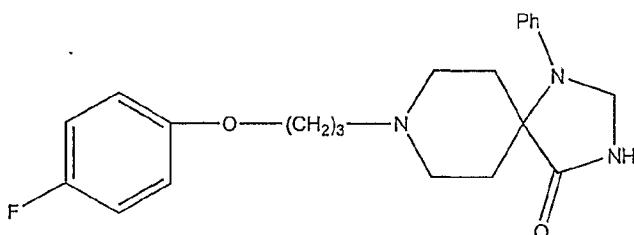
The most preferred 5-HT₃ receptor antagonist is tropanyl-3,5-dimethylbenzoate.

According to the present invention several known substances are, unexpectedly, able to enhance a 5-HT-induced airway smooth muscle relaxation by blocking the constricting 5-HT₂ receptor. Such antagonists are selected from the following groups and substances: Ketanserin, i.e. 7-azido-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]-ethyl]-6-iodo-2,4(1H, 3H)-quinazolinedione, having the structural formula:



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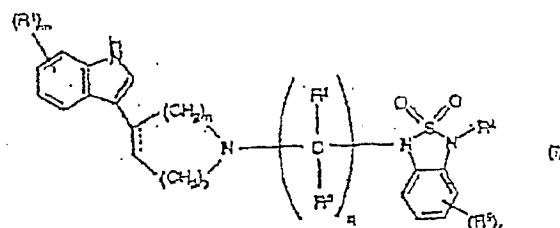
AMI-193, i.e. 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, having the structural formula:



5

1-((indolyl azacycloalkyl)alkyl)-2,1,3-benzothiadiazole 2,2-dioxides with the following structure, (see WO 00/49017)

10



15

thiopyran derivatives represented by the following formula (I) or (I'), or the salt thereof, (see US 6,100,265).

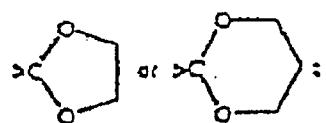
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wherein A is S or -CH=CH-; the dotted line indicates that the bond may be either present or absent; Z and Z' are typically

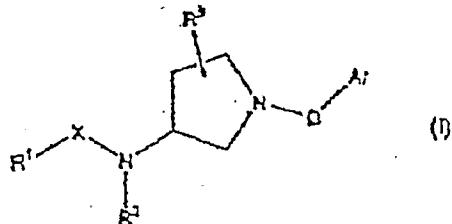
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L is an ethylene or trimethylene group; Y is CH or N; n is 2; B is a carbonyl group; m is 0 or 1; D is a phenyl group; and E₁ and E₂ are hydrogen atoms;

5 pyrrolidine compounds with the following structure:
(see WO 00/26186)

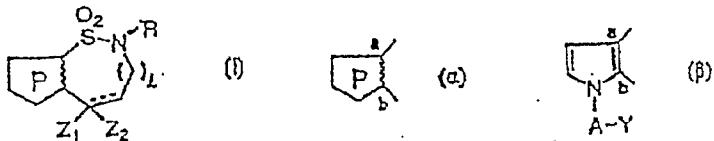
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15

Pyrrolothiazine and pyrrolothiazepine compounds (see
EP 0 970 089)

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25



30

(a) pyrrolesulfonamide compound having formula (I)
wherein the ring P represented by α is a pyrrole ring
having structure β or ψ wherein A represents alkylene,
alkenylene or alkynylene; and Y represents a group δ in
which W represents CH, C= or N; m stands for 0 or 1 when
W is CH or N, or m stands for 1 when W is C=; B repre-
sents a specific divalent group; E₁ and E₂ each indepen-
35 dently represents H or lower alkyl; and D represents an
aromatic hydrocarbon group or heterocyclic group; ℓ
stands for 0 or 1; the dashed line indicates the presence

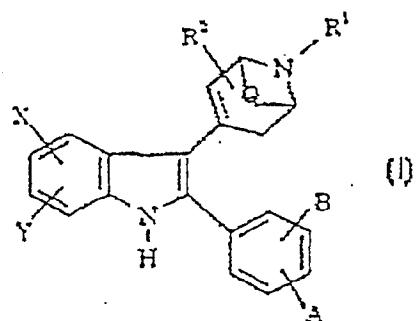
118

or absence of a bond; and, when the bond is present, Z_2 is not present and Z_1 represents H but, when the bond is absent, Z_1 represents H and Z_2 represents OH or Z_1 and Z_2 are combined together to represent O or a group NOR₅, in which R₅ represents H, or alkyl, aralkyl or aryl; and R represents H, alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl.

5 Azabicycle-substituted phenylindole derivatives with the following formula (see WO 00/04017).

10

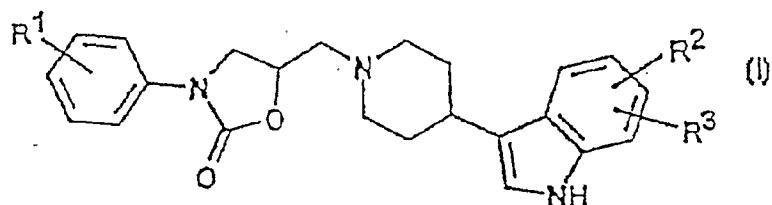
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Oxazolidines (see EP 0 964 863)

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Pyrrolothiazine and pyrrolothiazepine compounds (see EP 0 970 088)

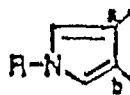
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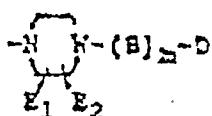


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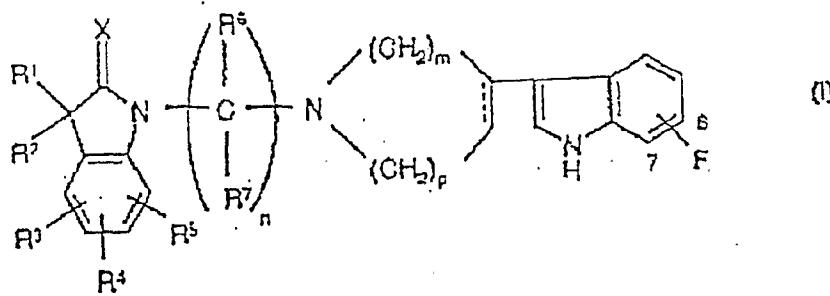
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(a pyrrolesulfonamide derivative having formula (I) wherein the ring P represented by α is a pyrrole ring having structure β or ψ wherein R represents alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl; the dashed line indicates the presence or absence of a bond; and, when the bond is present, Z_2 is not present and Z_1 represents H but, when the bond is absent, Z_1 represents H and Z_2 represents OH or Z_1 and Z_2 are combined together to represent O or a group NOR₁, in which R₁ represents H, or alkyl, aralkyl or aryl; ℓ stands for 0 or 1; A represents alkylene, alkenylene or alkynylene; and Y represents a group 1 in which W represents CH, C= or N; m stands for 0 or 1 when W is CH or N, or m stands for 1 when W is C=; B represents a specific divalent group; E₁ and E₂ each independently represents H or lower alkyl; and D represents an aromatic hydrocarbon group or heterocyclic group), indole derivatives with the following structures, (see WO 99/58525 and WO 00/49017).

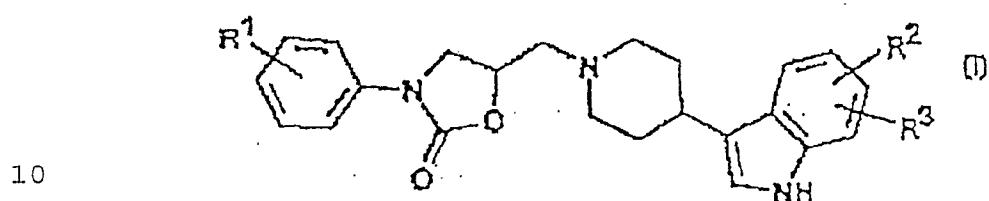


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preferably 3-(piperidin-3-yl)-1 H indole compounds (see WO 99/47511).

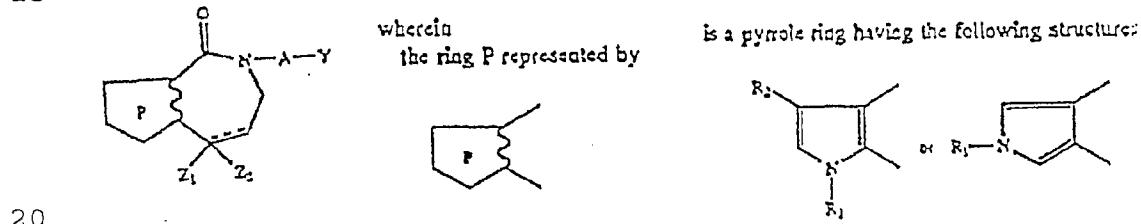
oxazolidine compounds (indole compounds) with the following structure (see WO 98/38189).

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pyrroloazepine compounds with the following structures, (see US 5,962,448).

15



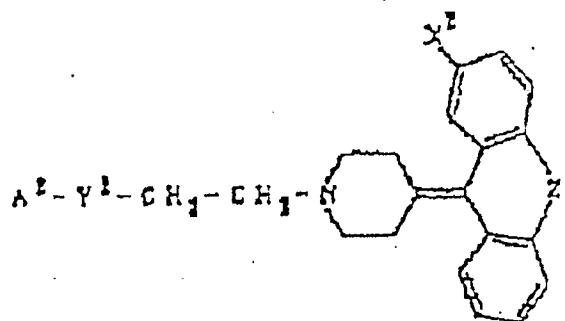
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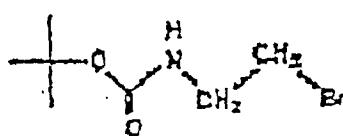
piperidine derivatives (see JP 11246526).

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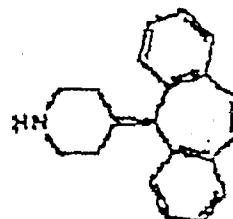


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II

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III

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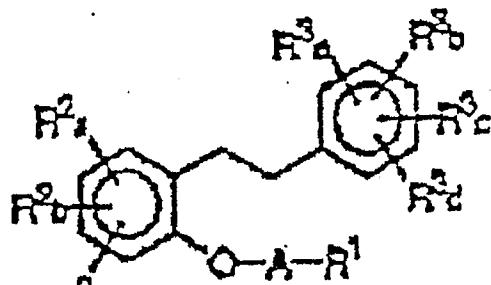
pyrrole sulphonamide-based compounds, (see JP 11193290),

25 substituted 1,2,3,4-tetrahydronaphthalene derivatives, (see EP 0 888 319), preferably piperidinyl and piperazinyl substituted 1,2,3,4-tetrahydronaphthalen compounds,

benzothiazine derivatives, (see US 5,874,429)

30 2-{2-[4-fluoro-2-(2-phenylethyl)phenoxy]ethyl}-4-hydroxy-1-methylpyrrolidine (see JP 11158067).

35



and biphenyl derivatives, (see US 5,849,912).

and ALEPH-2, amperozide, amesergide, aryloxyalkyl-imidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1 H)-one, CGS 18102A, cinanserin, clonidine, cyproheptadine, deramciclone, desmethyl-WAY 100635, dotarizine, DV 7028, elymoclavine, fananserin, 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine, 8-[3-(4-fluorobenzoyl)-propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, hexahydrocarbazoles, (3H)WAY 100635, ICI 169,369, 8-[3-(4-iodobenzoyl)-propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, LEK-8804, loxapine, LSD, LU 111995, LY53857, (S,S)-LY-53,857, (R,S)-LY-53,857, (S,R)-LY-53,857, (R,E)-LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, Metergoline fenylmethyl ester, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, methysergide, Mianserin, NE-100, N-desmethylclozapine, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquincline, NRA0045, olanzapine, ondansetron, 1-(2-pyrimidinyl)piperazine derivatives, pirenpirone, pizotifen, pizotyline, promethazine, raclopride, roxindole, risperidone, ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like flucxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, sulpride (±)-, fluvoxamine, spiro indoles N-substituted with a 3-(dimethylamino)propyl chain, spiperone, SR 46349B, thioridazine, WAY 100635, WY-50,324, MDL 100,907.

The most preferred 5-HT₂ antagonist is 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine.

The most preferred compositions according to the present invention are the following, in each example named in the following order:

5-HT₄-receptor agonist, 5-HT₃-receptor antagonist, 5-HT₂-receptor antagonist,

- RS67333 and 3-(1-piperazinyl)-2-quinoxalinecarbonyl nitrile and 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- VB20B7 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- RS67333 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and AMI-193
- VB20B7 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and AMI-193
- 10 - RS67333 and tropanyl 3,5-dimethylbenzoate and 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- VB20B7 and tropanyl 3,5-dimethylbenzoate and 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- RS67333 and tropanyl 3,5-dimethylbenzoate and
- 15 AMI-193
- VB20B7 and tropanyl 3,5-dimethylbenzoate and AMI-193
- RS67333 and VB20B7 and AMI-193
- RS67333 and VB20B7 and 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- 20 - RS67333 and 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole and AMI-193
- VB20B7 and 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole and 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- 25 The present invention also relates to a method for treatment of disorders involving airway constriction, wherein said method comprises the administration to a human or animal patient of a therapeutically effective amount of a composition comprising a combination of a) a compound with agonist activity to the 5-HT₄ receptor, b) a compound with antagonist activity to the 5-HT₃ receptor, and c) a compound with antagonist activity to the 5-HT₂ receptor. Preferably, said method relates to the treatment of asthma, chronic bronchitis, emphysema and chronic obstructive pulmonary disease.
- 30
- 35

The typical daily dose of the medicament prepared according to the invention varies within a wide range and

will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition
5 adapted either for administration via the respiratory tract or for oral, intravenous, intramuscular, subcutaneous, intrathecal, topical, or intraperitoneal administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are
10 well known in the art.

Said medicament is preferably administered via the respiratory tract in the form of e.g. an aerosol or an air-suspended fine powder. However, in some cases useful alternative administration forms are tablets, capsules,
15 powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories.

Detailed Description of the Invention

The subject-matter of the present invention was inter alia deduced from animal experiments, where a
20 specific behaviour of the airway smooth muscle called "spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in the airway smooth muscle, was studied due to a suspicion that a defective regulation of the spontaneous tone could
25 be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "Regulation of spontaneous tone in guinea pig
30 trachea" by S. Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone in physiological conditions, and this
35 tone can be reversibly affected by administration of various substances.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from a specific type of airway epithelium cells, so-called neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin (5-HT), which activates 5-HT₂, 5-HT₃ and 5-HT₄ receptors, among several others. Additional experiments showed that when a small dose (1 μ M) of 5-HT was added to guinea pig airway smooth muscle preparations displaying a strong, smooth spontaneous tone, a transient contraction was observed. A contractile effect of 5-HT on airways has previously been reported, see e.g. Skogvall, S., Korsgren, M., Grampp, W., J. Appl. Phys., 86:789-798, 1999. However, when a large dose (100 μ M) of 5-HT was used, the spontaneous tone was, after a transient contraction, significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal (pre-treatment) level when 5-HT was removed. Thus, it has now unexpectedly been shown that 5-HT causes a contraction of guinea pig airways at low concentrations and a relaxation at high concentrations, i.e. a dual effect. Furthermore, it was found that the 5-HT_{2a} receptor antagonist ketanserin almost completely abolished the contraction but did not affect the relaxation, demonstrating that the contraction and relaxation was caused by activation of different receptors.

Similar experiments have also been performed on human airway preparations from patients undergoing lobectomy or pulmectomy due to lung cancer. In humans, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig: even as low a concentration as 1 μ M 5-HT induced a significant relaxation in preparations displaying a spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, our examinations of spontaneous tone on human *in vitro* preparations have shown that 5-HT indeed causes a contraction also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline (pre-treatment) level. The relaxation, which has a maximum after 10-15 min, disappears gradually during the following 30-45 min (see Fig 1). In contrast, in guinea pig trachea, the first 5-HT-induced effect is a contraction which reaches a maximum after approximately 10 min, and this is followed, within approximately 30 min, by a relaxation below the pre-treatment level. The transient nature of the 5-HT relaxation in human airways is most likely caused by a simultaneous activation of the fast relaxing 5-HT₄ receptor, and an activation of slower contracting 5-HT₃ and 5-HT₂ receptors. This is clear, because activation of the relaxing 5-HT₄ receptor by a substance that lacks 5-HT₃ and 5-HT₂ receptor activating properties (such as RS 67333), results in a relaxation that is persistent and not transient. Further, unspecific agonists, such as 5-HT, can cause a sustained relaxation if the constricting 5-HT₂ and 5-HT₃ receptors are simultaneously blocked.

Figure 1 depicts the effects of 5-HT and the selective 5-HT₄ agonist RS 67333 on spontaneous tone in a human airway preparation *in vitro*. Note that 5-HT only gives a transient relaxation, while the selective 5-HT₄ agonist causes a strong sustained relaxation.

In SU 1 701 320 it is suggested that 5-HT may be of use as an addition to standard beta2 receptor stimulation for the treatment of acute asthma attacks. No receptor mechanism for the effect of 5-HT is disclosed in that patent. However, from the presently described experiments it appears obvious that 5-HT alone is unsuitable as a

treatment for said diseases, because of the only transient relaxing effect by 5-HT (see Fig. 1). Also, reports from other groups indicate that 5-HT if anything tends to induce a weak bronchoconstriction rather than a relaxation in asthmatics (see e.g. Dupont et al. 1999, Eur Resp J 14:642-649 and Takahashi et al. 1995, Am J Respir Crit Care Med 152:377-380, which are incorporated herein by reference). If instead, according to the present invention, a composition comprising a combination of compounds that stimulates the relaxing 5-HT₄ receptor and blocks the contracting 5-HT₂ and 5-HT₃ receptors is given, the relaxing effect is persistent, and not transient. The action of this combination at three different receptors causes a greater airway relaxation than an action at only one or two receptors. Further, we have found that the most important contractile receptor in some individuals is 5-HT₂ and in others 5-HT₃, which necessitates a combination of blocking substances.

In summary, it has now been discovered that activation of the 5-HT₄ receptor results in relaxation, whereas activation of the 5-HT₃ receptor and/or the 5-HT₂ receptor results in contraction. The dual response to 5-HT is most likely a result of its agonist action on the relaxing 5-HT₄ receptor as well as on the contracting 5-HT₃ and 5-HT₂ receptors.

It was also deduced from these experiments that compounds with agonist activity to the 5-HT₄ receptor, administered together with compounds with antagonist activity to the 5-HT₂ receptor and compounds with antagonist activity to the 5-HT₃ receptor, therefore are useful as agents for treatment of disorders involving airway constriction, as defined above.

Thus, the present invention relates to a composition comprising a combination of compounds comprising a) at least one compound with agonist activity to the 5-HT₄ receptor, b) at least one compound with antagonist activity to the 5-HT₃ receptor, and c) at least one compound with

antagonist activity to the 5-HT₂ receptor as a medicament. The present invention also relates to the use of said composition for the manufacture of a medicament intended for treatment of disorders involving airway constriction, as defined above, whereby said composition has the strong bronchorelaxing effect of 5-HT but substantially no constrictor effect. The administration of the composition can be simultaneous or sequential. The compounds according to the present invention with agonist activity to the 5-HT₄ receptor may also be unspecific, e.g. 5-HT.

In said combination of compounds with 5-HT₄ agonist and 5-HT₃ and 5-HT₂ antagonist activity, the relative amount of either compound may vary. Typically, the 5-HT₄ agonist is given in a somewhat larger concentration than the 5-HT₃ and 5-HT₂ antagonists, which, in turn, are normally given in about equal concentrations.

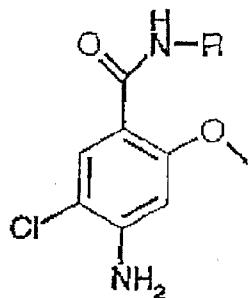
CLAIMS

1. A composition comprising a combination of a) at least one compound with agonist activity to the 5-HT₄ receptor, b) at least one compound with antagonist activity to the 5-HT₃ receptor, and c) at least one compound with antagonist activity to the 5-HT₂ receptor.

2. A composition according to claim 1, wherein said composition has the capacity of reducing pathological airway constriction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said combination is chosen from the following groups of 5-HT₄ agonists, 5-HT₃ antagonists and 5-HT₂ antagonists, or derivatives or pharmaceutically acceptable salts thereof:

a) 5-HT₄ receptor agonists: serotonin (5-HT) benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopramide, with the structural formula:

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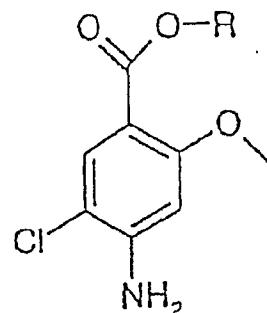
having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zucopride;

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130

benzoic acid esters:

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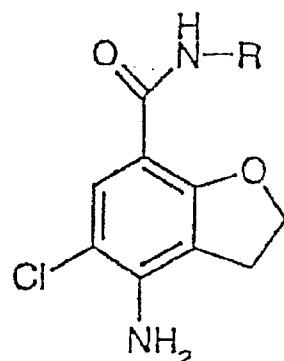


10

preferably ML 10302, RS 57639, and SR 59768;
 a 2,3-dihydro-benzo(furan-7-carboxamide compound,
 preferably ADR 932, Prucalopride (=R 093877), and SK-951;

15

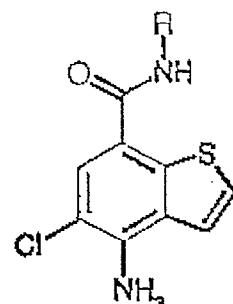
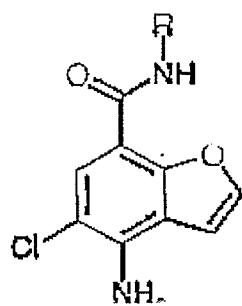
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benzofuranes and benzotriophenes,

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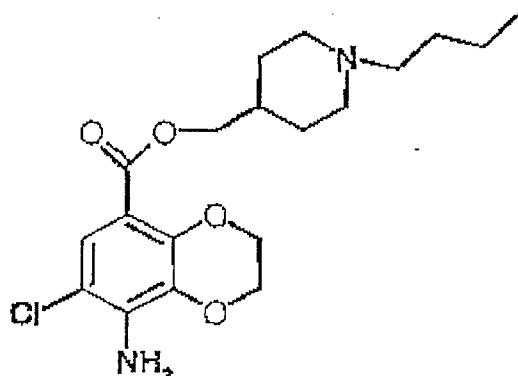


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131

the benzodioxan

5



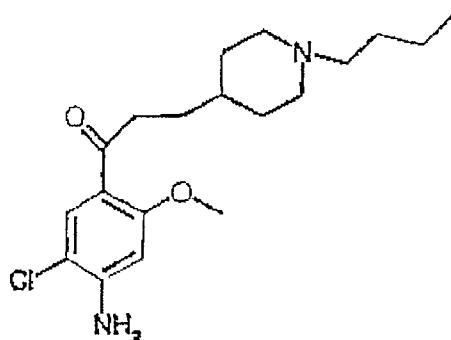
SB 204070

10

the benzoic acid antagonist RS 23597 (an ester)
transformed to an agonist by conversion to a ketone

15

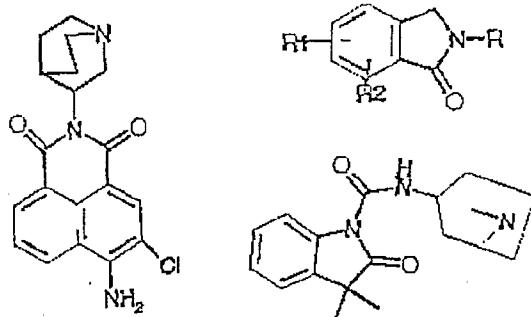
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e.g. preferably RS 67333 and RS 17017;
naphtalimides, preferably RS 56532;

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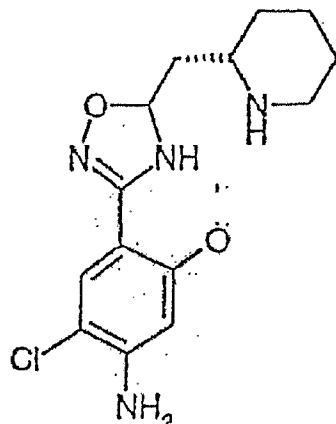
benzindolone;

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132

compounds in which the amide function has been replaced with an oxadiazol ring;

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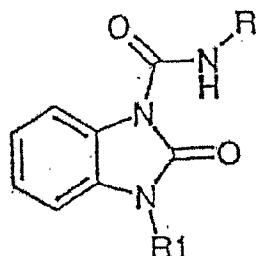


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preferably YM-53389;

15 benzimidazolone-1-carboxamides

20

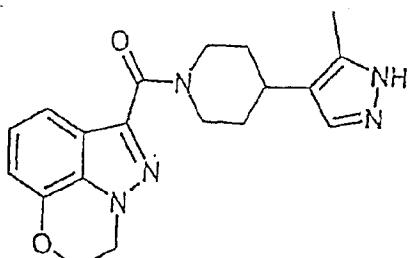
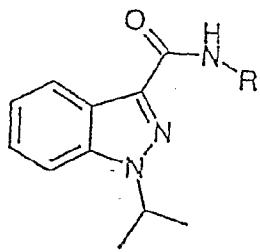


25

preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;

the carboamides

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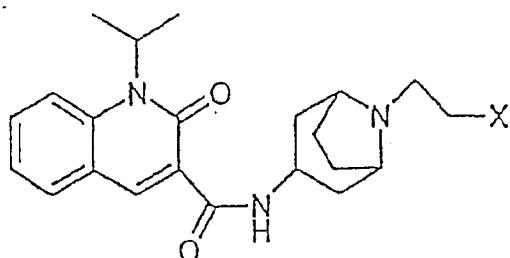
35

indols, preferably 5-methoxytryptamine, 2-methyl-
serotonin, and 5-hydroxy-N,N-di-methyltryptamine;

compounds quaternized on the nitrogen in the side chain:

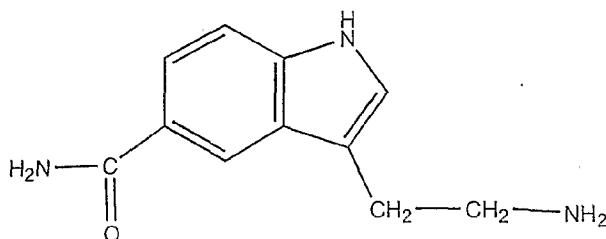
benzokinolinones

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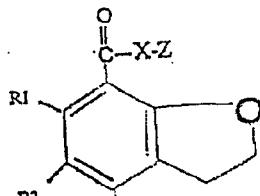
5-carboxamidotryptamine (5-CT), with the structural formula:



5-HT, 3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253,
 15 SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808,
 α -methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters,
 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxy-methyl-4-pyrrolidinyl)benzamide, thiophene carboxamide
 20 derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives,
 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzo-thiazole derivatives (e.g. VB20B7), Sandoz compound 1b,
 clebopride, 2-piperidinmethylethers of benzimidazole,
 zelmac, 2-[1-(4-piperonyl)piperazinyl]benzothiazole, benz-
 25 pyranes,

substituted dihydrobenzofuran derivates with the following structure:

30

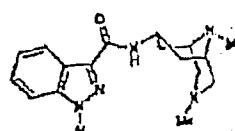
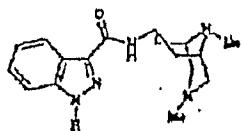


134

wherein R1-R3, X and Z are groups that can be substituted;

compounds with the following indazole structure:

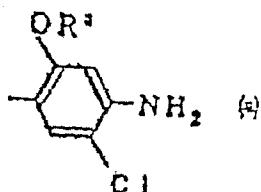
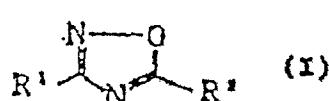
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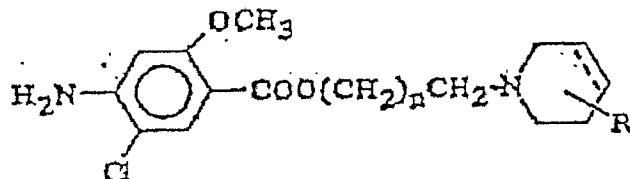
oxidiazole derivatives



15

4-amino-5-chloro-2-methoxybenzoic esters

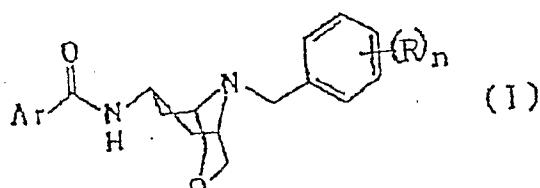
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(III)

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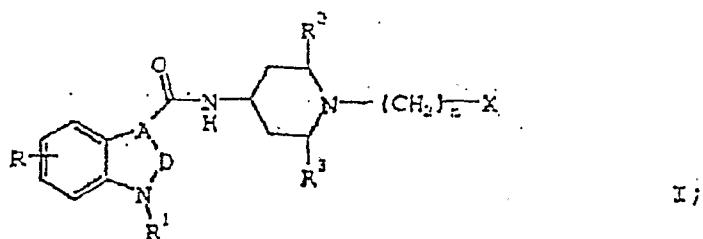
oxazabicyclo derivatives



30

compounds having the following structure

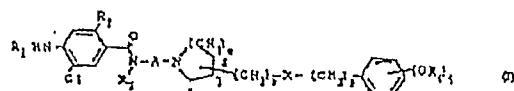
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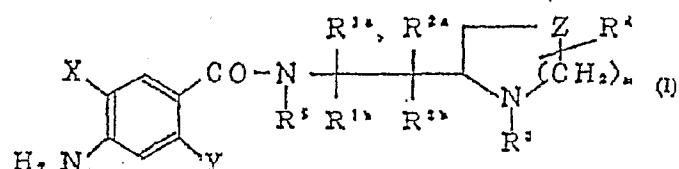
(I)

benzamide derivatives having the following structures

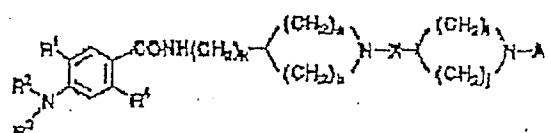
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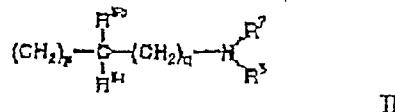
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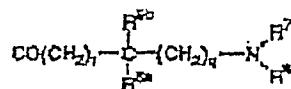
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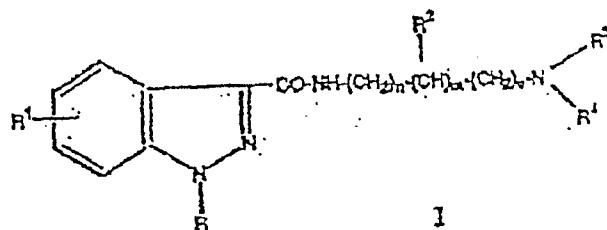
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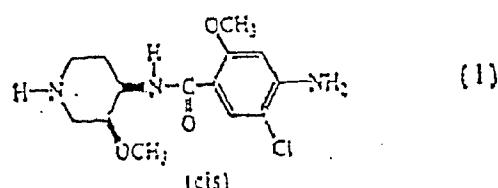
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indazolecarboxamides

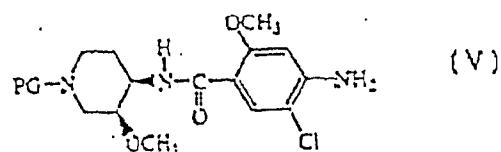
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(+)-norcisapride of formula (I) and compounds (V), and its pharmaceutically acceptable acid additions salts; compounds of formula (V) wherein the piperidine ring has the absolute configuration (3S, 4R) and PG is methyloxycarbonyl, ethyloxycarbonyl, tert-butyloxycarbonyl or phenylmethyl;



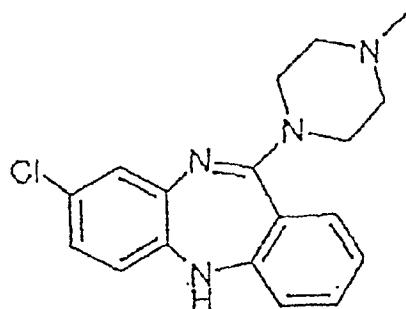
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20

b) 5-HT₃ receptor antagonists

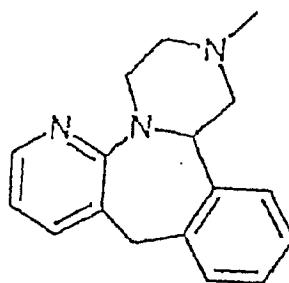
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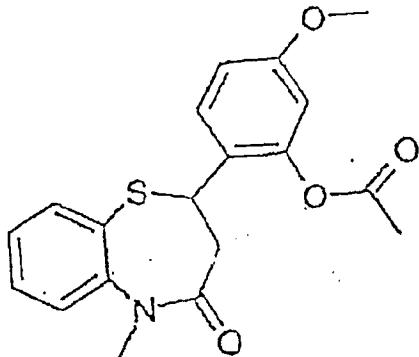
benzazepines, preferably mirtazapine

35



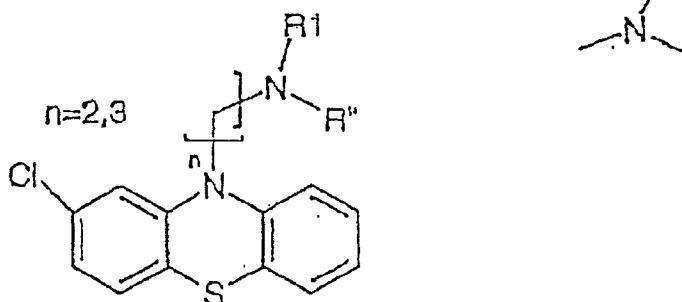
benztiazepines, preferably diltiazem

5



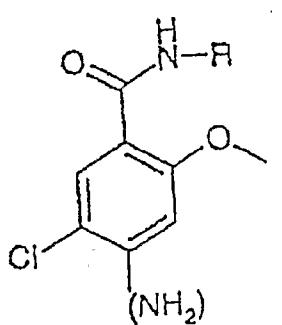
10 and fentiazines

15



20 preferably perphenazine, chlorpromazine, stemetil;
compounds also having 5-HT₄ receptor agonist activity, preferably benzamides

25

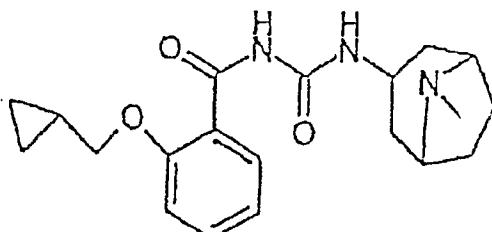


(cisapride, zacopride,
mosapride, metoclo-
pramide, pancropride,
BRL 24924, BMY 33462)

30

and

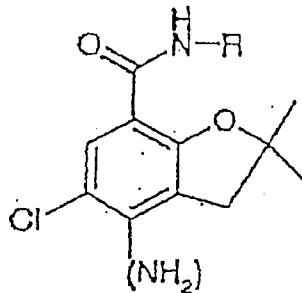
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WAY 100289

2,3-dihydro-benzofuran-7-carboxamides

5

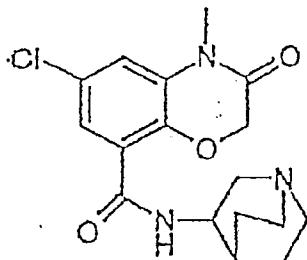


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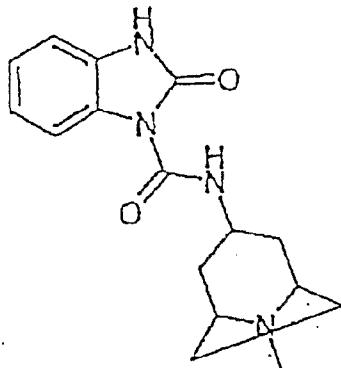
(preferably zatosetron=LY 277359, ADR 851);

1,4-bensoxazin-8-carboxamides

15

20 preferably azasetron (=Y25130);
benzimidazolones

25



30

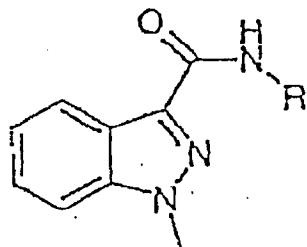
preferably itasetron (=DAU 6215);

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139

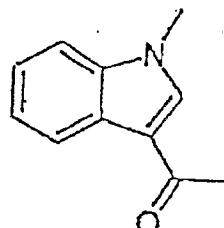
indazol-3-carboxamides

5



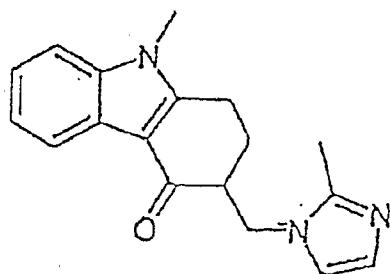
10 preferably N 3389, LY 278584, DAT 582;
 wherein the latter group reminds most of the
 specific 5-HT₃ antagonists, which contains the group

15



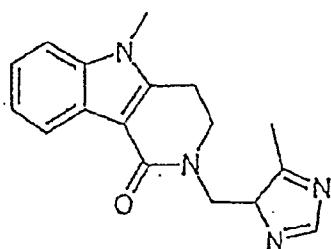
20 in different forms, such as

25



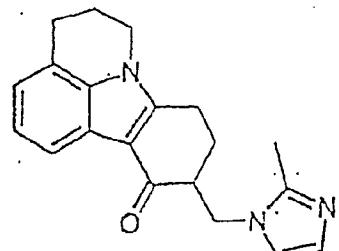
ondansetron

30



35

alosetron

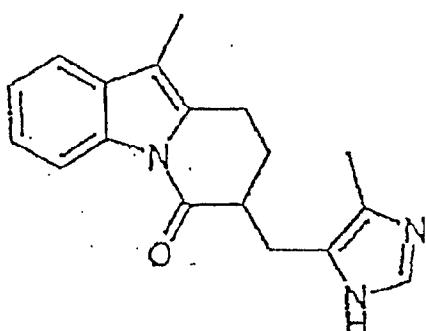


cilansetron

140

substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen

5



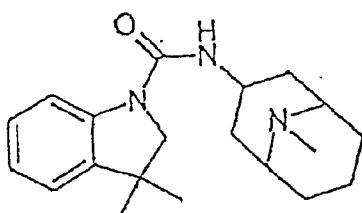
FK 1052

10

also being an antagonist against both 5-HT₃ and 5-HT₄ receptors,

15

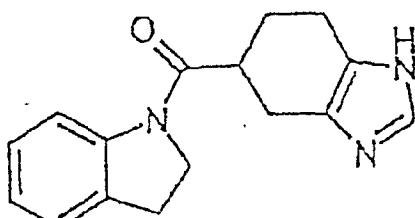
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BRL 46470 A

bisindoles

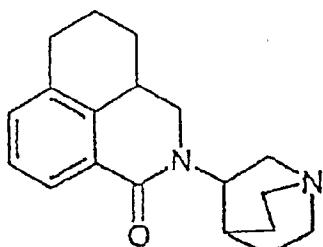
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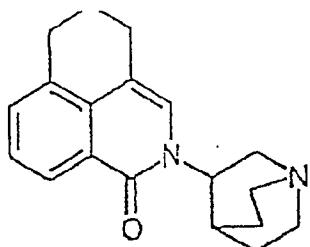
YM 114

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35



palonosetron (=RS 25259-197)

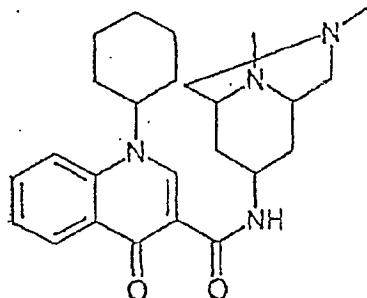


RS 42358-197

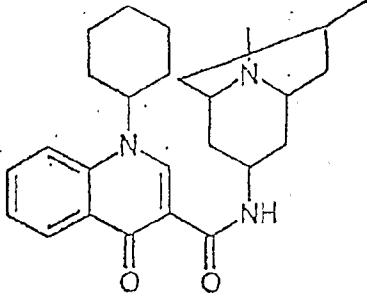
141

and the quinoline-3-carboxamides

5



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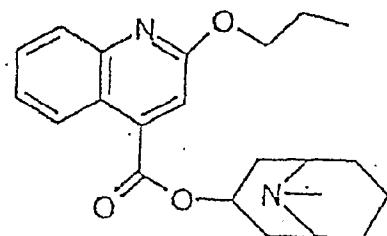
WAY-SEC 579

Mirisetron (=WAY 100579),

quinoline-4-carboxylates

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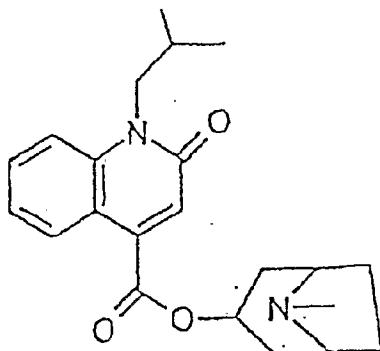
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preferably KF 17643

25

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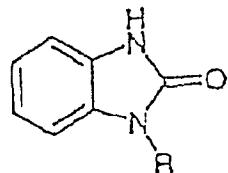


preferably KF 18259;

35

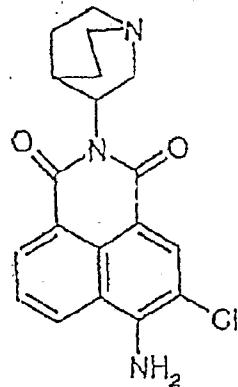
benzimidazolones

5



preferably droperidol (neurolidol), itasetron (DAU6215),
10 and the napthimidones

15



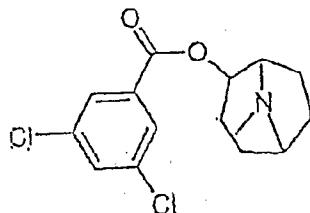
RS 56532

20

preferably RS 56532;

MDL 72222, which also is a specific 5-HT₃ antagonist;

25



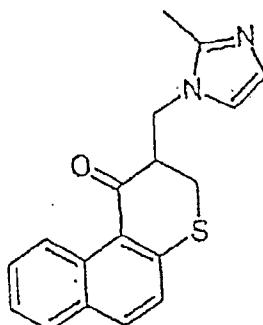
; and

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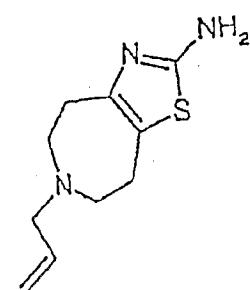
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GK 128

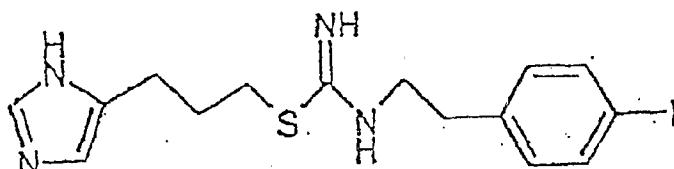
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Talipexole

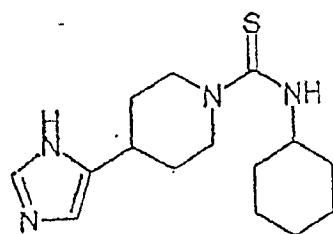
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iodophenpropit

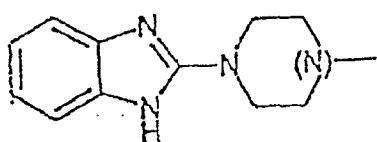
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thioperamide, and

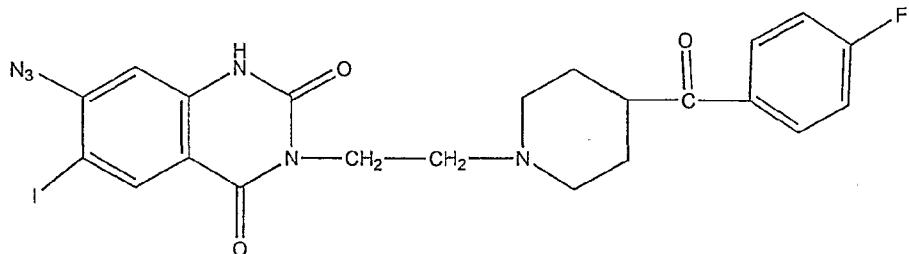
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2-piperidin- and 2-piperazin-
benzimidazoles; and also

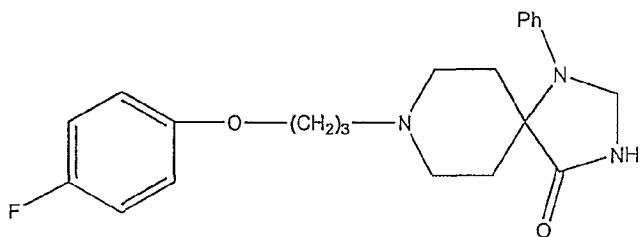
(R)-zacopride, 2-methyl-5HT, 3-(1-piperazinyl)-2-
quinoxalinecarbonitrile, 3-(4-allylpiperazin-1-yl)-2-qui-
noxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethyl-
amino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole,
5 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-
3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, AS-5370,
Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470
(=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM),
Cizapride, Clozapine, CP-93318, Cyameazine, Cyrohepta-
10 dine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone,
Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kyt-
ril=BRL 43694), GR-H, GYK1-48903, ICS 205-930, Imipra-
mine, Indalpine, KAE-393/YM-114, KB-6922, KB-6933,
KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458,
15 LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699,
Mepyramine, Metergoline, Methysergide, Mianserin, MK 212,
N-3256, NAN-190, N-methylquipazin, 3-(1-piperazinyl)-2-
quinoxalinecarbonitrile, ONO-3051, Pancopride, Phenyl-
biguanide, Pitozifen, Prochlorperazine, QICS 205-930,
20 R(+)zacopride, Renzapride, RG 12915, Ritanserin,
RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zaco-
pride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792,
SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322,
SDZ 322, SN-307, TFMPP, TMB 8, trifluoperazine, tropanyl-
25 3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate
methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A,
Pizotifen, Dolasetron (=MDL 74156), Galanolactone,
GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine,
QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525,
30 Trimebutine, GR 65630, Tropisetron, Bemesetron,
L-683,877, LY-278,584 maleate and pharmaceutically
acceptable salts thereof with the same or essentially the
same relaxation enhancing effect, and

c) 5-HT₂ receptor antagonists: Ketanserin, i.e. 7-azido-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-6-iodo-2,4(1H, 3H)-quinazolinedione, having the structural formula:



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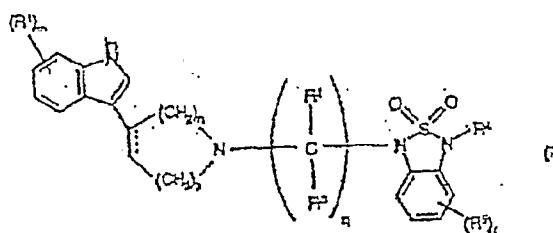
AMI-193, i.e. 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, having the structural formula:



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1-((indolyl azacycloalkyl)alkyl)-2,1,3-benzo-thiadiazole 2,2-dioxides with the following structure:

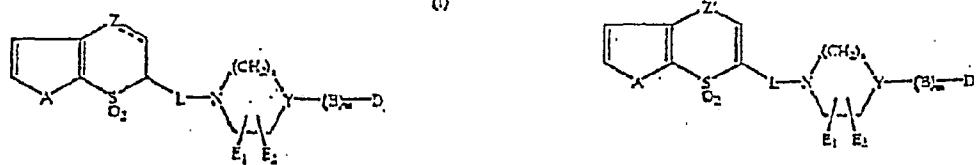
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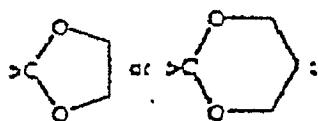
thiopyran derivatives represented by the following formula (I) or (I'), or the salt thereof:

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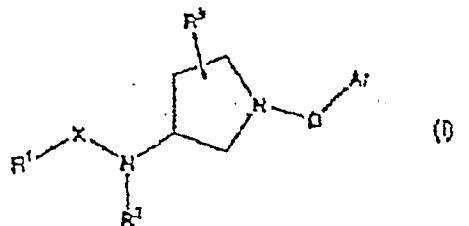
wherein A is S or -CH=CH-; the dotted line indicates that the bond may be either present or absent; Z and Z' are typically

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10 L is an ethylene or trimethylene group; Y is CH or N; n is 2; B is a carbonyl group; m is 0 or 1; D is a phenyl group; and E₁ and E₂ are hydrogen atoms, pyrrolidine compounds with the following structure:

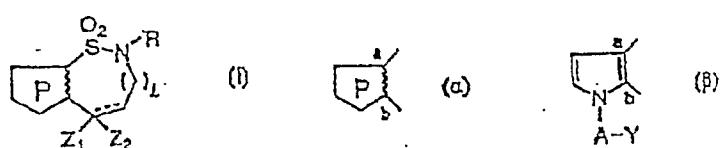
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pyrrolothiazine and pyrrolothiazepine compounds

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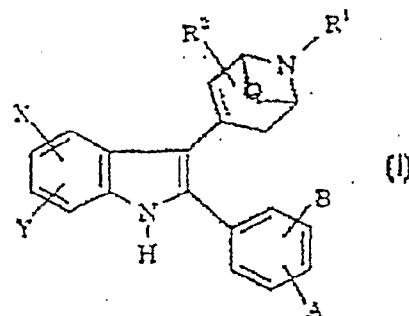
35 (a) pyrrolesulfonamide compound having formula (I) wherein the ring P represented by α is a pyrrole ring having structure β or ψ wherein A represents alkylene, alkenylene or alkynylene; and Y represents a group δ in which W represents CH, C= or N; m stands for 0 or 1 when

147

W is CH or N, or m stands for 1 when W is C=; B represents a specific divalent group; E₁ and E₂ each independently represents H or lower alkyl; and D represents an aromatic hydrocarbon group or heterocyclic group; l stands for 0 or 1; the dashed line indicates the presence or absence of a bond; and, when the bond is present, Z₂ is not present and Z₁ represents H but, when the bond is absent, Z₁ represents H and Z₂ represents OH or Z₁ and Z₂ are combined together to represent O or a group NOR₅, in which R₅ represents H, or alkyl, aralkyl or aryl; and R represents H, alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl;

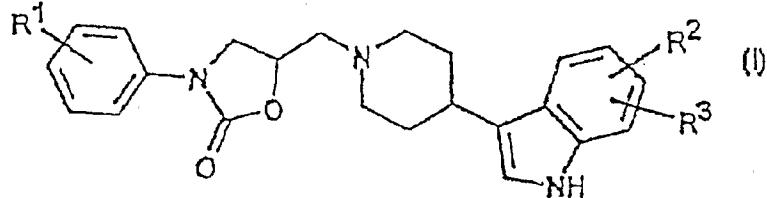
azabicyclic-substituted phenylindole derivatives with the following formula.

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oxazolidines

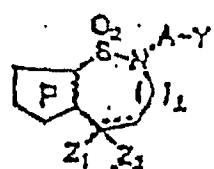
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pyrrolothiazine and pyrrolothiazepine compounds

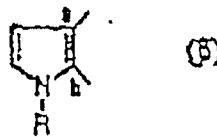
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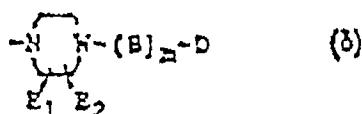
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(a)



(6)

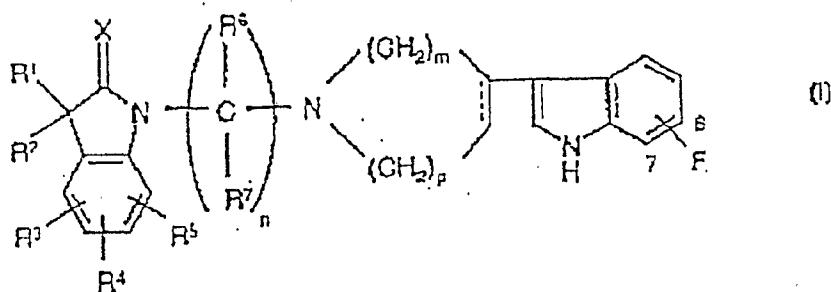


(7)

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(a pyrrolesulfonamide derivative having formula (I) wherein the ring P represented by α is a pyrrole ring having structure β or ψ wherein R represents alkyl, 15 cycloalkyl, cycloalkyl-alkyl or aralkyl; the dashed line indicates the presence or absence of a bond; and, when the bond is present, Z_2 is not present and Z_1 represents H but, when the bond is absent, Z_1 represents H and Z_2 represents OH or Z_1 and Z_2 are combined together to represent O or a group NOR₁, in which R₁ represents H, or alkyl, aralkyl or aryl; ℓ stands for 0 or 1; A represents alkylene, alkenylene or alkynylene; and Y represents a group 1 in which W represents CH, C= or N; m stands for 0 or 1 when W is CH or N, or m stands for 1 when W is C=; B represents a specific divalent group; E₁ and E₂ each independently represents H or lower alkyl; and D represents an aromatic hydrocarbon group or heterocyclic group), 20 indole derivatives with the following structures.

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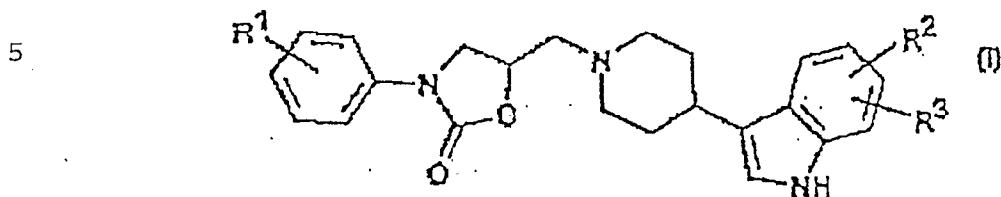


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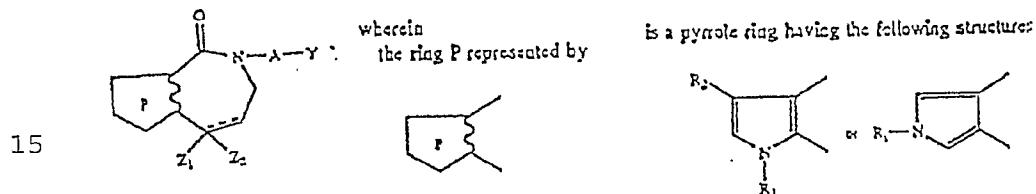
preferably 3-(piperidin-3-yl)-1 H indole compounds,

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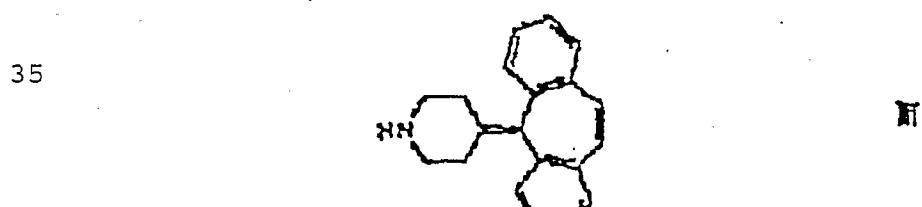
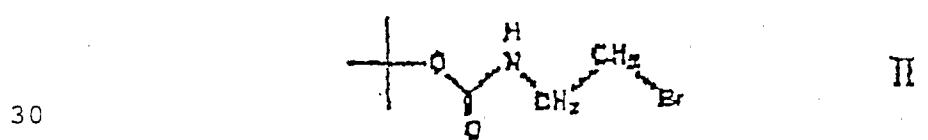
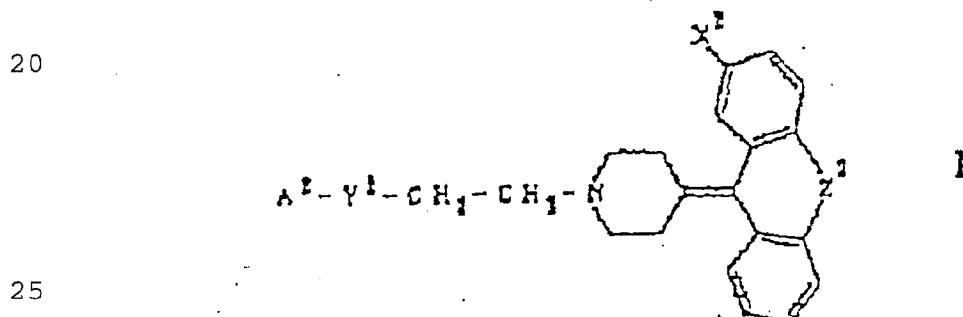
oxazolidine compounds (indole compounds) with the following structure



10 pyrroloazepine compounds with the following structures:



piperidine derivatives



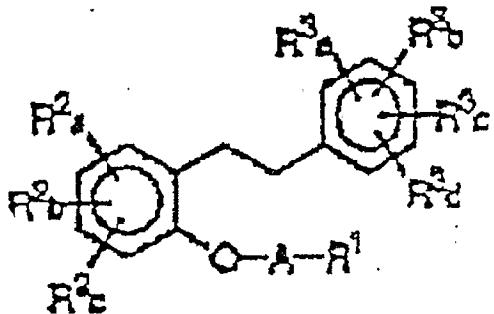
pyrrole sulphonamide-based compounds, substituted 1,2,3,4-tetrahydronaphthalene derivatives,

5 piperidinyl and piperazinyl substituted 1,2,3,4-tetrahydronaphthalen compounds,

benzothiazine derivatives,

2-{2-[4-fluoro-2-(2-phenylethyl)phenoxy]ethyl}-4-hydroxy-1-methylpyrrolidine

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and biphenyl derivatives, and ALEPH-2, amperozide, amesergide, aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl-6-fluoroindolin-2(1 H)-one, CGS 18102A, cinanserin, clonidine, cyproheptadine, deramciclane, desmethyl-WAY 100635, dotarizine, DV 7028, elymoclavine, fananserin, 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine, 25 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro-[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, hexahydrocarbazoles, (3H)WAY 100635, ICI1169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, LEK-8804, loxapine, LSD, LU 111995, LY53857, 30 (S,S)-LY-53,857, (R,S)-LY-53,857, (S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, Metergoline fenylmethyl ester, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, 35 methysergide, Mianserin, NE-100, N-desmethylclozapine, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, olanzapine, ondansetron, 1-(2-pyrimidi-

nyl)piperazine derivatives, pirenpirone, pizotifen, pizotyline, promethazine, raclopride, roxindole, risperidone, ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, sulpride (\pm)-, fluvoxamine, spiro indoles N-substituted with a 3-(dimethylamino)propyl chain, spiperone, SR 46349B, thioridazine, WAY 100635, WY-50,324, 10 MDL 100,907.

3. Composition according to claim 2, wherein it comprises a combination of compounds selected from one of the following combinations:

- RS67333 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- VB20B7 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- RS67333 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and AMI-193
- 20 - VB20B7 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and AMI-193
- RS67333 and tropanyl 3,5-dimethylbenzoate and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- VB20B7 and tropanyl 3,5-dimethylbenzoate and 4(4-25 fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- RS67333 and tropanyl 3,5-dimethylbenzoate and AMI-193
- VB20B7 and tropanyl 3,5-dimethylbenzoate and AMI-193
- RS67333 and VB20B7 and AMI-193
- 30 - RS67333 and VB20B7 and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- RS67333 and 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole and AMI-193
- VB20B7 and 5-((dimethylamino)methyl)-3-(1-methyl-1H-35 indol-3-yl)-1,2,4-oxadiazole and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine

4. Composition according to claim 2 for use as a medicament.

5. Composition according to claim 3 for use as a medicament.

5 6. Use of a composition comprising a combination of compounds comprising a) at least one compound with agonist activity to the 5-HT₄ receptor, b) at least one compound with antagonist activity to the 5-HT₃ receptor, and c) at least one compound with antagonist activity to 10 the 5-HT₂ receptor for the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction, chosen from the group consisting of asthma, emphysema, chronic bronchitis and chronic obstructive pulmonary disease.

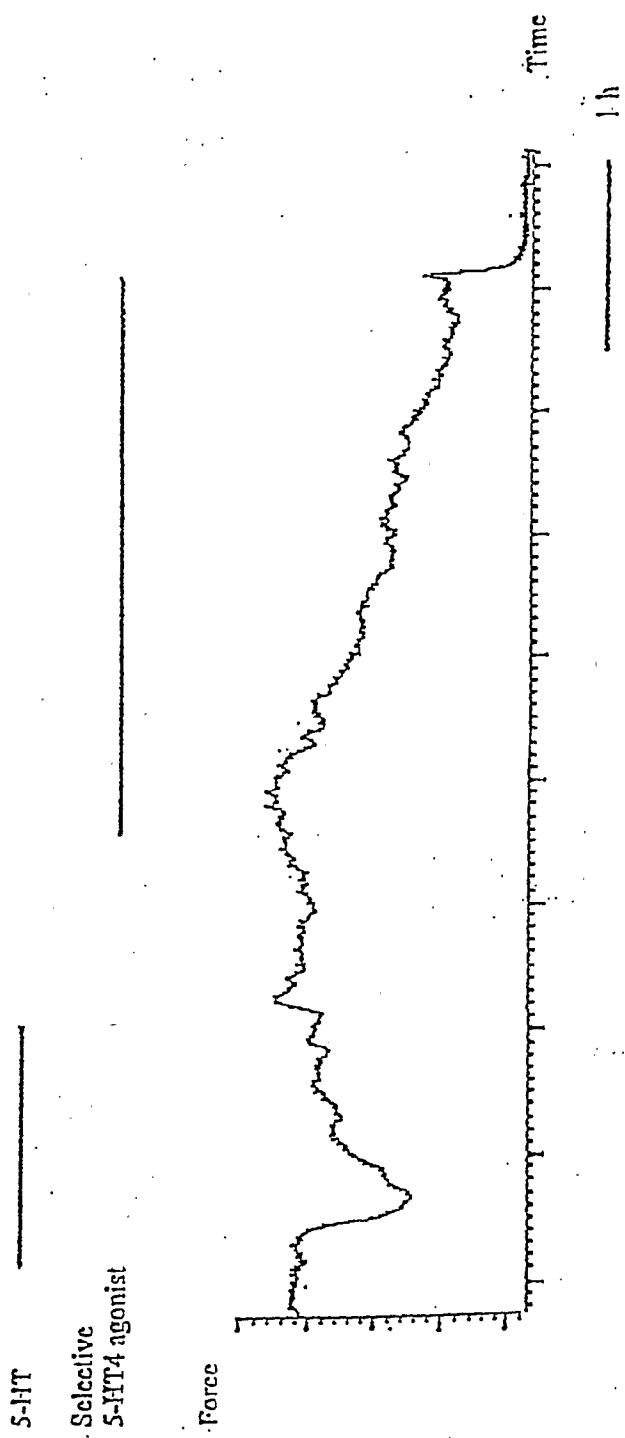
15 7. Use according to claim 6, of a composition as defined in claim 2.

8. Use according to claim 7, of a composition as defined in claim 3.

9. A method for the treatment of disorders involving 20 airway constriction chosen from the group consisting of asthma, emphysema, chronic bronchitis and chronic obstructive pulmonary disease, wherein said method comprises administration of a therapeutically effective amount of a composition according to any one of claims 1-3.

1/1

Fig 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/02372

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395, A61K 31/4045, A61P 11/06, A61P 11/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0076500 A2 (RESPIRATORIUS AB), 21 December 2000 (21.12.00), claims 1-17 --	3,5,8
X	J. Med. Chem.,, Volume 36, 1993, A. Monge et al, "Novel Antagonists of 5-HTs Receptors. Synthesis and Biological Evaluation of Piperazinylquinoxaline Derivatives", page 2745 - page 2750, page 2747 --	3,5,8
X	ES 2042395 A1 (PROMOTORA CATALANA DE INVERSIONES GENERALES, S.A.), 1 December 1993 (01.12.93), table 1 --	3,5,8

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2002	15-02-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Fernando Farieta/EÖ Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No. PCT/SE 01/02372
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9943319 A1 (THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS), 2 Sept 1999 (02.09.99), claim 3 --	3,5,8
X	Eur Respir J, Volume 14, 1999, L.J. Dupont et al, "The effects of 5-HT on cholinergic contraction in human airways in vitro", page 642 - page 649, figure 4 --	3,5,8
X	Chem. Pharm. Bull., Volume 48, No 5, May 2000, Akira Mizuno et al, "Synthesis and Serotonin 2(5-HT2)Receptor Antagonist Activity of 5-Aminoalkyl-Substituted Pyrrolo(3,2-c)azepines and Related Compounds", page 623 - page 635 --	3,5,8
X	J. Med. Chem., Volume 35, 1992, Jeff L. Herndon et al, "Ketanserin Analogues; Structure-Affinity Relationships for 5-HT2 and 5-HT1C Serotonin Receptor Binding", page 4903 - page 4910, page 4905 (Results), page 4909 (Compound) --	3,5,8
A	TiPS, Volume 21, June 2000, Andrew G. Ramage, "Central 5HT 1A receptors and vagal tone to the airways" page 201 - page 203 --	3,5,8
A	Clinics in Chest Medicine, Volume 10, No. 1, March 1989, C. Michael Hart et al: "Lung Serotonin Metabolism", page 59 - page 70 --	1-9
A	US 5977099 A (VICTOR JOHANNES NICKOLSON), 2 November 1999 (02.11.99), claims 1-13 --	1-9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02372

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>The Journal of Pharmacology and Experimental Therapeutics, Volume 257, No. 1, 1991, Carl K. Buckner et al: "A Pharmacologic Examination of Receptors Mediating Serotonin-Induced Bronchoconstriction in the Anesthetized Guinea Pig", page 26 - page 34</p> <p>--</p> <p>-----</p>	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/02372

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **1, 2, 4, 6, 7**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.: **9**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/02372

Box I.1

The claims contain a plurality of different compounds and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT such an extent that a meaningful search of the whole scope of the claims is impossible.

Expressions such as "compound with agonist activity to a 5-HT4 receptor" or "at least one compound with antagonist activity to a 5-HT3 receptor" or "at least one compound with antagonist activity to a 5-HT2 receptor" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Consequently, the search has mainly been carried out for those parts which appear to be clear, supported and disclosed, namely claim 3 and those parts of claims 5 and 8 relating to claim 3.

Box I.2

Claim 9 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/02

International application No.

PCT/SE 01/02372

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0076500 A2	21/12/00	AU 2016000 A AU 5259100 A AU 5861900 A EP 1152834 A SE 9902251 D WO 0064441 A AU 2016100 A EP 1135683 A SE 9902252 D SE 0000819 D	03/07/00 10/11/00 02/01/01 14/11/01 00/00/00 02/11/00 19/06/00 26/09/01 00/00/00 00/00/00
ES 2042395 A1	01/12/93	ES 1020127 U,Y	16/05/92
WO 9943319 A1	02/09/99	EP 1066036 A EP 1077678 A US 5942243 A WO 9958110 A	10/01/01 28/02/01 24/08/99 18/11/99
US 5977099 A	02/11/99	AU 727851 B AU 2612997 A BR 9703624 A CA 2208199 A CN 1173330 A CZ 9701870 A EP 0813873 A HU 9701068 A IL 121076 A JP 10067663 A NO 972816 A NZ 328113 A PL 320628 A SG 60073 A TR 9700522 A	04/01/01 08/01/98 01/09/98 19/12/97 18/02/98 14/01/98 29/12/97 28/08/98 31/10/00 10/03/98 22/12/97 29/09/99 22/12/97 22/02/99 00/00/00